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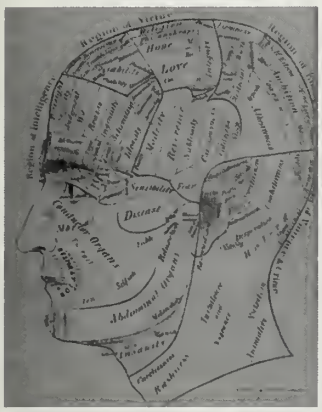
# Harvard Medical
## ALUMNI BULLETIN



***On the cover***
**Outlines of Phrenology by Joseph R. Buchanan, circa 1854. Courtesy of Rare Books, Countway Library.**

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# Inside BULLETIN@WARREN.MED.HARVARD.EDU

Harvard Medical
ALUMNI BULLETIN

"Information superhighway" is an oxymoron, as anyone knows who rode and remembers the old highways. Two-lane, routed right through the middle of town, occasionally peppered with Burma-Shave signs—these roads were remarkable for the sheer information in them. What child of the '90s can play alphabet or word games on an interstate? What driver has even a notion of where she is, except for the uniform white-on-green signs sparsely identifying numbered exits? Who could ever stop to ask?

In other ways, of course, the term is apt. Like real superhighways, the "Net" serves mainly to speed transit between two areas of congestion. Information must eventually take an off-ramp to enter the bumper-to-bumper tangle of someone's brain. With any luck it gets parked, and one remembers where.

All in all, I resist fantasies of an electronic *Alumni Bulletin*. Print, paper and portability make the format comfortable for my aging eyes and helter-skelter schedule. The limitation of space imposes a certain discipline on content (though it also forces us to make hard choices as to what among the riches we are offered we can hope to print).

That said, my colleagues and I at *HMAB* would very much like to learn whether we're missing the electronic boat.

Would anyone who can please drop us a line at BULLETIN@WARREN.MED.HARVARD.EDU?

We have no idea, within even an order of magnitude, how much e-mail this request will generate. That's something we'd like to know. (Indeed, there's a small office pool riding on the outcome.) We'd also like to know your name, class and location. Would you like a computer bulletin board allowing you to communicate with other HMS alumni? Is there something we can offer you electronically that we can't provide on paper? We don't guarantee an e-answer, but please watch this space for more about alumni communication at millenium's end.

*William I. Bennett '68*



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# Letters

**Dissent in the House**

The Summer '94 issue of the *Bulletin* highlighting "The Writers Among Us" is a grand one. The talents on display affirm the long-held axiom that Harvard Medical School attracts the best and brightest of multipotential young people.

Among those writers featured is Stephen J. Bergman '73, author of, under the pseudonym Samuel Shem, *The House of God* (Dell, 1978). When I read the book 15 years ago, I was offended and angry. Now, having read his essay in the current *Bulletin*, I feel obliged to take up my less skillful pen.

In his current work as teacher of third-year medical students, Bergman finds affirmation of the "insensitivity, rough authority, brutality and outright cruelty" he described so vividly in *The House of God*, and now claims is a pervasive pattern of behavior by the clinical faculty in their treatment of clinical clerks.

As a surgical resident at the MGH (1956 to 1958) and Children's Hospital (1958 to 1961), my experience was so different as to bear some description and, I would hope, offer rebuttal to *The House of God*, whose abuses exist in the mind of Bergman and a few other dissidents, but not in the main body of house pupils, past and present from the Harvard hospitals. Most are proud of their appointments, proud of the splendid faculty assembled to instruct them, and proud of the supervised responsibility placed in their hands to aid the sick. Insensitivity on the part of some individuals? Yes. Arrogance in an instructor or a professor? Yes. Occasional harassing abuse of authority by an attending? Yes. However, as Bergman fails to observe, those unpleasant traits of behavior are extant throughout society and occur neither more nor less frequently in health care education.

Memory of my own training years begins with Dr. Edward D. Churchill, great chief of surgery at the MGH. World renowned for innovative surgical research, he exhibited gentleness at the patient's bedside, warmth to the students and residents, and pride in and support of the legion of pupils he nourished. Dr. Churchill's disciples became an assemblage of professors and practitioners of surgery across the land and beyond. They did not see nor exhibit the inhumanity that Bergman would have us believe is rampant in Harvard medical education. In fact, it was from a phalanx of Churchill-trained surgeons that I learned reverence for life and respect for the human body, concepts that Bergman claimed were nonexistent in the thinly veiled Harvard hospital he labeled the "House of God."

Across town, at the Children's Hospital, we would have endured any abuse from Dr. Robert E. Gross to learn the craft of children's surgery from him. But there was no abuse. Hard work, expectation of excellence, and intolerance of mediocre effort abounded. These guidelines were not to further an academic reputation nor to demean an assistant, they existed for one purpose: to get desperately ill children well. Some students and a number of residents in financial straits found money in an envelope in their box with a little note of encouragement, signed R.E.G.; blatant paternalism perhaps, but hardly insensitivity.

In the *Bulletin* essay, Bergman refers repeatedly to a "power-over" institution he found odious as an intern. The only power I noted amongst my clinical teachers was their power of knowledge and expertise, which they strove usually with patience and always with dedication to impart.

A second charge Bergman makes is that the residency teaching system he encountered "effectively isolated us from one another," which he asserts encouraged unhealthy faculty dominance since, he writes, "the enemy of dominance is the quality of the connection among those dominated." Such pejorative observations sound more like fodder for civil revolt than curriculum revision. During nine exciting years at Harvard, I saw hundreds of students, residents and fellows who were highly talented, basically happy and committed beyond all else to increasing their own knowledge on behalf of those patients they would one day serve. In the exigencies of a crowded emergency room, or a midnight crises on the ward, junior members of the health care team formed alliances, friendships and interdependencies that encouraged humanism at the highest level.

How could Bergman's experience at Harvard and mine have been so different? It cannot be ascribed to the 15-year interval that separates our training days. I know many of the current teachers in the Harvard hospitals, some of whom shared night call with me. It is not different now. I conclude that Stephen Bergman, perhaps a successful writer, is carrying a flag for the few and not the many in the Harvard medical education experience.

*Judson Randolph*
*Nashville, Tennessee*

**In Response**

I appreciate the time and sensitivity that led Dr. Randolph to write a response to my article. His experience as a surgical resident in the 1950s sounds wonderful. I wish I'd had that experience in the 1970s. If I had, I wouldn't have had to write my novel. *The House of God* has sold over a million copies. Though it doesn't speak to Dr. Randolph, it does speak to doctors

# Letters

and medical students across a broad range of geography, ethnicity, class and race.

Or *does* it speak to Dr. Randolph? Of my writing that "the enemy of dominance is the quality of the connection among those dominated," Dr. Randolph says, "Such perjorative observations sound more like fodder for civil revolt than curriculum reform." Thank you, Dr. Randolph, for seeing what I meant. Given a choice between transformation ("civil revolt") from a power-over to a shared-power system, or curriculum reform, I would take the former—with the faith that curriculum reform would soon follow.

*Stephen Bergman '73*
*("Samuel Shem")*

**Experiences Shared**

I read Stephen Bergman's "*The House of God:* A Historical Perspective" (Summer '94) with great interest.

His question "How do we stay human in medicine?" is one that I have been thinking about for years. It is especially important to me as an anesthesiologist practicing in a high-tech environment, where often my very reason for being is to render patients unconscious. I have brought my need to stay human into my work in our pre-admission test area, where anxious patients welcome my verbal ministrations. I have also channeled this need into action by successfully launching a newsletter for my alumni/ae organization (Boston University School of Medicine). The driving force behind the newsletter is to explore how our alumni/ae have answered this question.

Is reflection on the physician's need to stay in touch with his or her humanity a developmental phase of being 40-something, of coming of age in the 1960s, or of acknowledging a call to our innermost spirits, which maturity enables us to articulate? The positive response to my newsletter indicates to me that many physicians appreciate discussion of this heretofore guarded topic.

I also find it fascinating that Bergman's specialty is addiction medicine. I have devoted the past one and one-half years of my professional "free time" to learning about addictions. The practice of addiction medicine is one of the few branches of medicine where attention is paid to spirituality. It is the only specialty where patients and their doctors are permitted, in fact encouraged, to admit powerlessness over disease. Training programs in "power-over" institutions either omit this lesson of powerlessness in other disease states or massively deny that any doctors trained in their hallowed halls are powerless over anything.

Finally, one rule from *The House of God* has been my companion since 1978, and I'm happy to have the opportunity to thank the author "in person." That rule is that at a cardiac arrest, the house officer should take his own pulse first. It is impossible to take good care of patients unless we first take good care of ourselves. "HALT" is universally applicable, even if it means 10 seconds to assess your own anxiety level before pumping on a chest.

I applaud the *Bulletin's* publication of this article and hope to see more articles on how we teach students and residents the value of retaining their humanity in practice environments that seem to be more interested in outcomes and economics than retaining the "tender, loving care" aspects of medicine.

*Mary Kraft*
*Anesthesia Medical Director, MGH*

**Emergency?**

The letter to the editor by Patricia Glowa "Family Matters" (Autumn '94) resonated strongly with my own experiences at Harvard Medical School, but from a slightly different perspective—emergency medicine rather than family medicine.

I remember when I told my faculty advisor that I intended to pursue emergency medicine, it was almost as if I had died. Surely I understood the folly of straying outside the boundaries of legitimate medical study? When I graduated in 1981, there was no formal emergency medicine at HMS or any of the affiliated hospitals, a situation that has not changed substantially. There are some nascent efforts, but they are largely unsupported.

Emergency medicine, however, has not stood still. It has matured as a specialty beyond expectations. And, like family medicine, there is and will continue to be a need for academic and clinical practitioners that far exceeds the supply. Where do you think government training dollars might flow?

As serendipity would have it, the Autumn issue of the *Bulletin* arrived nearly simultaneously with a letter to the alumni from Daniel C. Tosteson '49, dean of the Faculty of Medicine. Dean Tosteson devotes the middle of his letter to a celebration of the diversity at HMS—both of students and faculty. He writes "The incoming class of 1998 is the most diverse ever... The School is greatly enriched by this diversity, and we take pride in knowing that we are a beacon for top students who come from every walk of life."

Sadly, it seems to me, and I believe Dr. Glowa might agree, that the notion of diversity at HMS means taking "top students who come from every walk of life" and ensuring that they all turn out the same.

It has been three years since I left private practice to join the faculty in the Department of Emergency Medicine at Johns Hopkins University School of Medicine. Did it really take 10 years for me to learn that emergency medicine is a legitimate field of study?

*Tempus fugitum est*, indeed!

*Edward S. Bessman* '81

*The school has just adopted a proposal to initiate a division of emergency medicine, whose purpose will be to coordinate teaching, research and patient care in this field among the school and its affiliated hospitals.* —Eds.

**More in an Oath**

My pleasure in reading the *Alumni Bulletin* was greatly enhanced by finding the article by Nathaniel Hupert '94 entitled "What's in an Oath" (Autumn 1994). As a student and teacher of medical ethics for almost 20 years, I have collected oaths and codes enunciated by various health professional groups. In 1976 I facilitated the creation of an oath by the graduating Child Health Associate students at the University of Colorado Health Sciences Center in Denver.

I applaud the creators of the oath that is presented in Hupert's article. Of special merit was Hupert's explication of the oath, with an emphasis on "humane education of future doctors" and "virtues they should cherish in themselves."

There is an area of human experience that has deliberately been omitted by the authors of this oath; namely, "references to God, gods or other religious figures." Certainly I would not have us return to invoking Apollo, Asclepius, Hygieia and Panaceia to begin the oath. I agree with Hupert's position that to invoke any explicitly religious images would be inappropriate and potentially offensive to our pluralistic religious community. My concern is the unnecessarily nihilistic approach taken by Hupert, et. al., in which possible dependence on "divine support" is transmuted into "focus on the secular issues." I would choose to focus on spirituality and spiritual realms of discourse, rather than on gods and religion.

The spiritual facets of people's lives must be addressed in health care so that we can indeed practice in a whole-person centered manner. The seminal quotation given to me in my first year at HMS was by Francis W. Peabody: "One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient."

In his book *Patient as Person*, Paul Ramsey points to the spiritual nature of patients: "Just as man is a sacredness in the social and political order, so he is a sacredness in the natural, biological order. He is a sacredness in bodily life. He is a person who within the ambiance of the flesh claims our care. He is an embodied soul or ensouled body." Ramsey avers that the practice of medicine is a covenant in which physician and patient relate faithfully to each other.

What I want to highlight in this letter is the shifting paradigm in health care from a dualistic, mechanistic, reductionistic model of patients to a biopsychosocial model, which treats patients as whole persons. Matthew Fox, in his recent book, *The Reinvention of Work*, opens our vision with the notion, "A veteran in his profession was suggesting that were we to rediscover the sacredness of the body, our medical profession could become less competitive, less greedy, and less expensive. The key is beginning with the sense of joy and sacredness."

One of my medical heroes is Albert Schweitzer, who gave up a number of promising careers in order to practice medicine in an African jungle. In a paean to Schweitzer, Norman Cousins says, "Albert Schweitzer is a spiritual immortal. We can be glad that this is so. Each age has need of its saints. A saint becomes a saint when he is claimed by many men as their own, when he awakens in them a desire to know the best that is in them, and the desire to soar morally."

Finally, I would suggest to Hupert, et. al., that they could initiate their oath with the phrase, "I do solemnly swear by whatever I hold most sacred..." This would not only be inoffensive to any specific religious group, but would also provide a sacred undergirding to their oath. This could set the stage for physicians to "soar morally" in the care of patients as whole persons.

*Thomas C. Washburn* '57

## Erratum:

**Due to last-minute rushing, the *Bulletin* incorrectly identified Elena Martinez in a photo from the women's dinner in the Autumn '94 issue. The photo is of Cheryl White '97. We apologize for any confusion this may have caused.**

# Pulse

**Kirks Becomes Kirkpatrick Professor**

Donald Kirks, radiologist-in-chief at Children's Hospital, has been named the first recipient of the John A. Kirkpatrick Professorship in Radiology. The chair, established in March, is funded by Children's Hospital.

Kirkpatrick, who died in May after a long illness, was chairman of the Department of Radiology at Children's Hospital from 1974 until his retirement in 1992. He was highly regarded for his skills as a diagnostician and for his excellence as a teacher.

Kirks succeeded Kirkpatrick as radiologist-in-chief at Children's. Kirks is a specialist in the research of emergency chest radiology of infants and children, and in the evaluation of chest masses and abdominal imaging. He has written more than 220 papers and his textbook *Practical Pediatric Imaging: Diagnostic Radiology of Infants and Children* is currently in its second edition.

At the reception, Kirks described his plans to strengthen the radiology department at Children's through emphasizing the importance of teaching and research. He is eager to have the staff at Children's begin "setting frontiers" in pediatric radiology.

"This is certainly my proudest academic moment," Kirks said. "But there is a responsibility that goes with that, a responsibility to the tradition of excellence that John set up in this department. It's difficult to follow a legend."

**Building Bridges on Mental Health**

When a final blueprint for a reformed health care system surfaces, those charged with providing and overseeing mental health resources hope their patients will be adequately funded. To insure that communication pathways remain open between Washington and mental health care facilities and service programs, the "Bridges" program of the Department of Health Care Policy brought together senior government policy makers and academics in December to discuss the issues and to plan for the future.

Howard Goldman '74, professor of psychiatry and director of Mental Health Services Research at the University of Maryland School of Medicine in Baltimore, delineated the key debate by highlighting the peculiarities in funding mental health services, which isolate mental health from other disease categories: one-third of the funding comes from state and local

**Donald Kirks**

photo by Barbara Steiner

expenditures, the majority of funding is private, and a "huge differentiation of function" exists.

His point was further clarified by Thomas McGuire, professor in the Department of Economics at Boston University. The problem, he said, is that the majority of those using ambulatory mental health services do not fit into disease categories. This discrepancy "highlights a problem if general workers are paying for services used disproportionately by a few upper income individuals."

The round table around which decision makers were sitting easily facilitated dispute on this issue, by which one participant argued that 80 percent of these patients missed a DSM-III diagnosis by one symptom. But this was only the beginning, as several issues surrounding terms like carve-outs, capitation, something called "soft capitation," utilization control and cost sharing and block grants sparked debate throughout the day.

No one denied that mental health care is expensive and multi-faceted. "Mental health/substance abuse users are bad risks in an insurance sense," said McGuire. In addition, the most severely affected also weigh down society with other costs, such as housing or criminal costs. The arguments are who pays and how, who assumes more risk—the insurance companies, the providers or the patients— and who receives services—those who really need them or those who can afford them? These are the dilemmas imbedded within what Richard Frank, HMS professor of health economics in the Department of Health Care Policy, called the "murky area" of managed care.

"The prize in this game, and it's a negative prize, is who gets to pay for the psych hospital," said McGuire. "The Fed moved first to not pay for the prize." This means, he continued, that states absorb this cost, but in order to pay their bills, they must engage in "cost-shifting"—a pea-under-the-nut shuffle game where state mental health agencies reappropriate federal funds for purposes for which they weren't intended.

The afternoon was devoted to policy makers from different states discussing what works and what doesn't in their states. In New Hampshire, a "city disguised as a state," where Thomas Fox is medical director of the division of mental health, there is a real attitude of partnership, he said, turning a phrase on the state's motto: "In mental health, if you try to live free, you die."

Due south, Annette Hanson, HMS lecturer on psychiatry and deputy commissioner for clinical and professional services for the Massachusetts Department of Health, discussed how her staff conducted focus groups of patients in the system to determine what they liked and didn't like, and then tried to fit policy and programming accordingly. In this state, said Hanson, comprehensive community support systems complement acute care services.

While much of the talk seemed disconcerting, especially in light of President Clinton's soundly defeated Health Security Act, Ellen Shaffer, legislative assistant from the office of Senator Paul D. Wellstone and the Senate Working Group on Mental Health, voiced optimism about what had been accomplished. "There was an acceptance by leaders in Congress that mental health is important." The fact that this support was bipartisan, she said, suggested that some of the stigma attached to issues of mental health had been assuaged.

"There is a good opportunity to feed information from groups like this to governors," said Thomas Romeo, executive in residence at the University of Rhode Island. "Part of the objective we should have in this Bridges group is to get policymakers interested in the issue."

# Pulse

Rachel Rohde, HST Society (left) and Ann Chen, Holmes Society.

photo by Barbara Steiner

**You've Come a Long Way, Baby**

"I never thought I'd see this in my lifetime," said Eleanor Shore '55, dean for faculty affairs, when she heard the news. "I absolutely could not have predicted this." She wasn't talking about a cure for cancer, a space mission to Mars or some other equally futuristic accomplishment. Shore was remarking on the incoming class of Harvard Medical School.

An unprecedented number of women and minorities compose the Class of 1998: of the 170 incoming students, 89 are women and 88 are nonwhite (45 are Asian American, 31 are African American and 6 are Latino).

"It shows the changing patterns of American society, and the willingness of Harvard Medical School to not only go with the flow, but to actively take part," said Alvin Poussaint, faculty associate dean for student affairs.

This class has created quite a stir, not just locally but nationally. HMS is part of a national progression towards diversifying the halls of medical education. Yale, Johns Hopkins and George Washington medical schools all announced that their incoming classes in 1994 have female majorities, while nationwide women make up roughly 40 percent of the 67,000 medical students currently enrolled.

Shore's surprise was well founded. In her day, 7 percent of HMS classes were women: "We were still part of the 10-year experiment," she said. That experiment had begun six years earlier when 12 women were permitted to enter the Class of 1949.

The next challenge, of course, is to create a faculty with an equally impressive representation of women and minorities. Currently 7.1 percent of HMS professors are women while 4.9 percent are minority. "Harvard Medical School has been steadfastly committed to affirmative action, to the recruitment of students drawn from segments of society not adequately represented in medicine," said Dean Daniel Tosteson '49. "While we take some modest pride in this accomplishment, we must not forget the need to be equally dedicated to the goal of similar diversity of our faculty."

HMS students come from around the country and around the world. For the 10th straight year, Californians and New Yorkers make up the largest percentage of incoming students. The farthest away from home, nationally, comes from Hawaii, while internationally, students come from as far away as


Kristin Upchurch, Peabody Society (left) and Rashel Feinstein, Castle Society.

photo by Barbara Steiner

photo by Barbara Steiner

**Kulleni Gebreyes, Castle Society.**

Oman, Sri Lanka and Yugoslavia. Thirty-three students came across the river from Harvard/Radcliffe, while 15 came north from Yale.

The majority of the incoming students are in their early 20s, with 55 aged 22 and 31 aged 23. A 21-year span, however, is represented with one student aged 18 and the oldest, 39. Not surprisingly, this class is the cream with 53 percent boasting a science undergraduate GPA of 3.75 to 4.0, and MCAT scores nearly 3 points above the national average.

**From the Heart**

Cardiologists are more likely than primary care physicians to prescribe effective drugs to patients who survive an acute myocardial infarction; and the number of invasive treatments performed on elderly patients who suffer acute AMI could be reduced by as much as one-quarter with no effect on overall survival outcomes. Those are the results of two studies developed by investigators from the Department of Health Care Policy at Harvard Medical School.

Led by John Ayanian '87, HMS assistant professor of medicine, researchers surveyed over 1,200 physicians from New York and Texas regarding their knowledge and prescribing practices of specific drug therapies for myocardial infarction. They were questioned about their likelihood to prescribe drugs whose effectiveness in overall survival has been shown in clinical trials—thrombolytic agents, aspirin and beta blockers—and about drugs that did not improve survival, and which may in fact be harmful, such as the prophylactic use of lidocaine.

Results indicate that family practitioners and internists were less informed about effective treatments for MI, and more apt to prescribe drugs that had not been proven to be beneficial. For example 94.1 percent of cardiologists reported that they were very likely to prescribe thrombolytic agents, compared to 77.3 percent of the family practitioners. Cardiologists also were more up to date on new information regarding ineffective treatments, as demonstrated by a 4.7 percent reported use of lidocaine compared to 16.7 percent by family practitioners. The study was published in the October 27 issue of the *New England Journal of Medicine*.

Ayanian says that the results of this study should impact managed care policies, which have encouraged a trend toward primary care physicians over specialists. "It's important to maintain a role for specialists to collaborate with physicians in primary care." The next step now is to look at actual treatment practices, a project that is just beginning.

Ayanian's study followed on the heels of another, which considered the effectiveness of invasive procedures, such as revascularization, catheterization and angioplasty, to treat acute myocardial infarction in the elderly. The study's authors—Mark McClellan '92, clinical fellow in medicine at Brigham and Women's Hospital; Barbara G. McNeil '66, Ridley Watts Professor of Health Care Policy; and Joseph P. Newhouse, John D. MacArthur Professor of Health and Policy—used a new tool in outcomes research called instrumental variables.

Clinical trials—the routine method of choice for testing treatment options—are difficult to perform on the elderly, expensive and often unethical. The authors argue that a reliable statistical approach, such as instrumental variables, may provide viable adjuncts for making therapeutic decisions. Unlike other analytical approaches, outcomes research incorporating instrumental variables empowers investigators to tease out those factors that affect disease outcome, such as co-morbid disease and severity of illness. "We tried to develop a method that was like a randomized trial, but used real world data," says McClellan. Their study was published in the September 21 issue of *JAMA*.

Examining Medicare claims data from 1987 through 1991, researchers discovered that hospitals that supported a high volume of catheterizations and other invasive procedures

were more likely to perform the operation than smaller, less modern facilities. The determining factor for whether a patient received invasive treatment was more a result of where that patient was admitted than the actual severity of his or her illness. Researchers found that one-fourth of the invasive procedures performed on elderly acute AMI patients could be eliminated and have no effect on survival. What most influenced longterm survival, as deduced from this method, was treatment AMI patients received within 24 hours following their attacks.

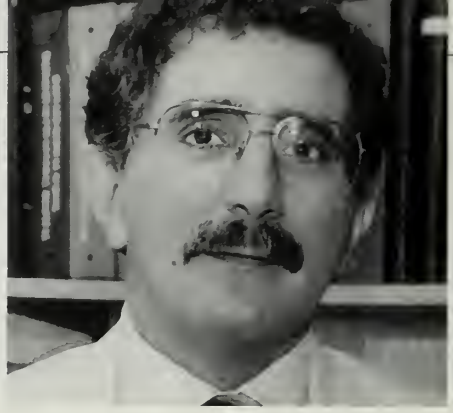
While the study doesn't mention specifically what these acute treatments are, the researchers did find a correlation between more technologically advanced hospitals and longterm survival. Advantages such a facility may include are greater use of thrombolytics or clot-busting drugs and a better trained emergency staff.

The study concludes by suggesting that a redirection of some resources from performing invasive procedures to these acute, noninvasive treatments more available could reduce costs while improving ami survival. It also suggests that invasive techniques for cardiac care might be regionalized to a few centers within a given area without affecting mortality.

"This method provides a fundamentally different approach to outcomes research, which will hopefully bring the debate about outcomes research to a new level," says McClellan.

The HMS Department of Health Care Policy is one of several PORTs, or Patient Outcomes Research Teams, working around the country. Established in 1989 by then Secretary of Health and Human Services, Louis Sullivan, with funding provided over the next five years by the HHS Agency for Health Care Policy and Research, PORTs were designed to "measure the effectiveness of alternative medical procedures in treating specific health conditions."

Part of the goal for the Harvard PORT is to not only determine which treatments for AMI are most effective, but also to ask, for example: "What is the effect of doing less of something versus more of something," says McNeil. In terms of making policy decisions, outcomes research provides fruitful answers.



David Herzog

photo by Barbara Steiner

**Eating Disorders Center Established**

The newly established Harvard Eating Disorders Center will bring together experts from a number of disciplines and Harvard institutions to combat eating problems that affect more than eight million young women and one million young men in America. The center will be led by David Herzog, associate professor of psychiatry. Herzog is the founder and director of the eating disorders unit at Massachusetts General Hospital. The center's projected opening date is January 1, 1995.

Dennis Ausiello

Richard Kitz

photo by S. Bray

**New Director of MD/PhD Program**

Dennis A. Ausiello, professor of medicine, is the new director of the MD/PhD program. Ausiello is also chief of the renal unit and vice chairman of the Department of Medicine at Massachusetts General Hospital. He replaces Gerald Fischbach, Nathan Marsh Pusey Professor of Neurobiology, who had been acting director since November 1993, when Bernardo Nadal-Ginard resigned.

The MD/PhD program, which currently enrolls 163 students, trains physician-scientists in both research and clinical care of patients. Students take courses offered at the medical school, the Faculty of Arts and Sciences and at MIT.

**A Dean for Clinical Faculty**

With an eye toward the changing clinical environment, Dean Daniel Tosteson '49 has created the position of faculty dean of clinical affairs and appointed to it Richard Kitz, Henry Isiah Dorr professor and former chairman of the Department of Anaesthesiology at Massashusetts General Hospital.

"Rapid and complex changes in the organization of the delivery of health services are generating opportunities and risks for Harvard Medical School and all of academic medicine," said Tosteson. Kitz's responsibilities will be to develop ways to mitigate the risks and take advantage of the opportunities. "Dick Kitz is superbly qualified to help the clinical faculty think through these issues."

Among Kitz's main responsibilities will be to mediate the conflictual relationships between managed care plans and the clinical faculty within the 17 affiliated hospitals, as physicians are pressed to meet clinical requirements at the expense of their teaching and research commitments.

"The control has shifted to a third party that doesn't have the same central mission that medical schools and academic hospitals have had. Most HMOs don't care about education," said Kitz.

Kitz will also begin thinking of ways to reconcile the relatively small number of residency slots open in primary care within the affiliated hospitals—currently, fewer than 10 percent—with the national call to train primary care physicians. He will also be working with Robert Glickman '64, Herrman Ludwig Blumgart Professor of Medicine, on a committee charged with investigating ways to strengthen residency training in clinical departments.

# On the Quadrangle

**Mapping the Mind**

Explorers of the brain and its behavioral manifestations come to the expedition with their own set of tools, with flashlights aimed at familiar terrain. To test the idea that new insights into society's problems may result from a meeting of usually disparate minds from the neurosciences, social sciences and humanities, the Mind/Brain/Behavior interfaculty initiative was launched two years ago. It is one of five themes that Harvard University President Neil Rudenstine designated for interfaculty pursuit; the others are children's education, ethics, the environment and health care.

As in the parable of the blind men who each felt different parts of an elephant and thought he knew what an elephant looked like, there is a risk that specialists can become overly isolated and blinded to the context of their exploration. MBB's mission, according to a steering committee statement, is "to overcome the steep walls of specialization" and "understand the forces that shape the human mind on all levels, ranging from molecules and genes, to synapses and circuits, to education and history."

Even the name of the initiative was carefully thought out: brain is in the middle and there is no "and" between brain and behavior so as not to be construed as an afterthought. For they wish to "create a community that will be energized by its interest in addressing questions that matter most to all involved, and in then trying on unfamiliar ideas and exploring novel connections to address those questions."

Two years since the "Noah's ark" of 21 faculty from nine of Harvard's schools first met, the MBB has evolved into a dynamic "faculty fellowship" of 24 who are palpably excited about what they are doing. They meet every couple of months for interactive dialogues. They have listened to each other expound, and have begun to pick up the nuances, the tools, the language of each other's approaches to such topics as memory, brain images in the Amazon, organizational learning, addiction, and the brain's anatomy and physiology. These are not just neurobiologists and psychologists; they are economists, historians, theologians, lawyers, philosophers, anthropologists.

"What feels magical to me," says Shawn Bohen, the administrative director of MBB, "is that the energy surrounding these interactions has been sustained. We seem to have struck on a content area and a process of interaction that has kept people on their toes and intrigued over the past two years."

Steven Hyman '80, HMS associate professor of psychiatry and neuroscience, has been named director of the initiative; Gerald Fischbach, Nathan Marsh Pusey Professor of Neurobiology continues as chairman of its steering committee. The key to the success of the endeavor, says Bohen, is the "idea of multiple levels of analysis" from "a broad representation of individual disciplines."

Because of the success of the project, people are clamoring to get involved. Appointment to the faculty fellowship is now for three-year terms to rotate membership. And there are additional tiers of participation. Conferences open to other faculty have been held—one on memory distortion last May and one on placebo in December. There is a committee studying undergraduate and graduate curricular development, and a graduate seminar on violence was offered.

The "intellectual engine" of the initiative is seven working groups, which have been created to consider questions in the realm of human behavior for which interdisciplinary thinking might yield strategies. Working groups at this point cover memory; symbolic behavior; drugs and addiction; intergroup violence; development of brain and behavior; experience of illness; and self-command, motivation, emotion.

The last group, for example, concerns itself with why we so often fail to learn from experience. As they have articulated their quest: "Why do people often act in ways that are inconsistent with what they mean to do, want to do and intend to do? Why don't people learn from their mistakes? Why do people engage in self-deception and defensive behaviors, get stuck and resist learning? Why do people hang onto bad theories?" One thing this group is exploring is how neural circuits associated with anxiety and fear might subvert more constructive learning strategies.

One future goal of the Mind/Brain/Behavior initiative is to establish a brain mapping laboratory, to take advantage of the unprecedented access to the inner workings of the brain that imaging technology now offers. This laboratory may be housed at the medical school when the old Boston English building is renovated; another "home" for the initiative will be on the Cambridge campus.

Those involved in this initiative hope that their effort can succeed where other mind-brain programs have come up short or failed to sustain involvement over time. MBB is considered a 10-year experiment in cross-disciplinary interaction and has ambitious goals. But they are counting on the commitment of the deans, intellectual rigor, and the breadth of "sustained dialogue" to "understand the vulnerabilities of our brain better, understand ourselves better and, in practical terms, formulate better policy."

*Ellen Barlow*

# President's Report

*by John D. Stoeckle*

The Alumni Council's first meeting of the 1994/95 school year focused on change at and around HMS.

William I. Bennett '68 was welcomed as the new editor of the *Alumni Bulletin*. The council, who has had ongoing, personal concerns about student financial aid, then heard good and bad news. From the Development Office (Kate Hill and Peter Nessen), came the good: in addition to raising $32,000 more than last year, the Alumni Fund, which has made student aid a priority, inspired an additional $1.3 million financial-aid dollars from nonalumni. The bad news came from Dan Federman's commentary that medical education is not getting cheaper. It costs $38,000 per year to attend HMS; 75 percent of students require financial aid, first as loans, some with supplemental scholarship money.

From the Admissions Committee, Gerald Foster '57 reported that the entering class is now 52 percent women, out of a growing, talented HMS applicant pool (3,111 and 3,425 in the last two years), which includes more minorities than ever. Not unexpectedly, more applicants are expressing an interest in today's theme of health reform—primary care.

From Continuing Education, Steve Goldfinger noted that the future may call for more education focused inside organizations and staff group practices. In order to more effectively change clinical decisions, courses may have to be more longitudinal and interactive than the many popular lecture courses of the current two- to five-day programs, which assuredly keep practitioners up-to-date in knowledge if not in performance.

Chairperson of the HMS Committee on Post-Graduate Education, Robert Glickman '64, noted that his committee is looking at post-graduate residency training, traditionally the exclusive domain of the individual hospitals. More combined/cooperative hospital experiences are being explored and planned, such as the recently designed residency program in emergency medicine.

The Alumni Fund will have new leadership with Cliff Barger '43A, who was elected unanimously its chair.

Finally, change is even going to be celebrated, not resisted, endured or scorned, as the council plans Alumni Day to address themes around women's health, in praise of that change of 50 years ago—the admission of women to HMS!

*John D. Stoeckle '47 is HMS professor of medicine emeritus, and physician, Massachusetts General Hospital.*

# Bench Marks

### It's All in the Eyes

A simple, noninvasive eye test is a promising premonition of Alzheimer's disease and, though results need to be replicated in larger trials, the test even appears to identify people pre-symptomatically.

In a preliminary study of 58 people, Harvard medical researchers identified those with Alzheimer's with at least 95 percent accuracy, by measuring hypersensitivity of pupils to a diluted concentration of the pupil-dilating drug, tropicamide. Their results were reported in the November 11 issue of *Science*.

Huntington Potter, associate professor of neurobiology at Harvard Medical School, came up with the idea for the eye test after perusing the literature on Down's syndrome. Those with Down's syndrome who live past age 30 develop the same brain lesions and suffer similar dementia as those with Alzheimer's. Potter, who believes that Alzheimer's might actually be a form of Down's, was looking for some kind of telltale marker associated with Down's that might also be present in Alzheimer's. In reading several reports that Down's patients are sensitive to drugs that block the effects of the neurotransmitter acetylcholine, he found his key. Alzheimer's patients are known to have low levels of acetylcholine.

He went to the Beth Israel's Marsel Mesulam, professor of neurology, who put him in touch with Leonard Scinto, lecturer on neurology (who is now at Brigham and Women's Hospital) and they developed an assay for the hypersensitivity, using a dilute solution of the acetylcholine-blocking drug, tropicamide. Acetylcholine signals the iris muscles to constrict. Scinto led the clinical testing of the eye test and is the lead author of the published study.

Of the 32 healthy people in the

study, 30 had no sensitivity to the diluted drug, but the pupils of 18 of the 19 previously diagnosed with Alzheimer's dilated 13 percent or more. One apparently healthy control who tested positive for Alzheimer's in fact was diagnosed with the disease nine months later; the two other "false-positives" reported in the study will be followed to determine if they ever convert.

"We seem to have hit upon something that occurs very early in the disease process," says Potter.

Although there are neurological and psychological tests to diagnose Alzheimer's, it is often misdiagnosed or confused with other causes of memory loss. It can really only be confirmed at autopsy by the presence of amyloid deposits and neurofibrillary tangles.

With Alzheimer's affecting more than 20 million people worldwide, the stakes to find a reliable diagnostic are high. There have been other hopeful tests in the past—blood tests, skin punch or brain scans—whose results did not hold up in large clinical trials.

Scinto is starting another clinical study in January 1995 with expanded numbers and scope to look at different strengths of the drug and at people with other neurological diseases that lead to dementia. He doesn't want to get his hopes up too much, but comments: "The striking nature of the initial data makes us hopeful. There was a clear separation between populations, which makes us feel that these solid results will hold up."

*Ellen Barlow*

**Brain Scanning for Strokes**

A means of arresting a stroke in progress may provide a therapeutic breakthrough in survival for the half million Americans who suffer a stroke every year, 150,000 of whom die. Researchers at Beth Israel Hospital and Children's are collaborating to test a combination of high-tech brain scanning techniques and drugs to halt neural damage.

The first step involves a package of software and hardware that "plugs into" MRI and increases the speed of this brain scanning hardware from several minutes to one-tenth of a second. Called echo planar imaging, which is enhanced by a software program called diffusion water imaging, this brain scanning technology basically provides "a way of looking at how the water molecules dance around in the brain," says Robert Edelman, HMS professor of radiology and director of MRI at Beth Israel Hospital. If a brain is experiencing a slow diffusion of water molecules, he explains, then the blood flow to the brain has been reduced and the person is in danger of developing a stroke.

Stroke research indicates that a stroke develops over several hours, not the few minutes originally thought. Provided the stroke patient enters the hospital in time, a window of opportunity exists for this type of rapid-result scanning to be performed. This neuroimaging strategy far exceeds those already in place, explains Edelman; a CT scan taken during a stroke will look normal for 12 hours and an MRI will look normal for 6 hours.

"But the time to prevent damage is in the first few hours. With diffusion water imaging, you can detect damage within minutes." When those who are in the process of experiencing a stroke are scanned, the image can relay the progression of neural damage already suffered and the amount of healthy tissue remaining.

The term "ischemic penumbra"—the latter borrowed from the field of astronomy—refers to the halo of still healthy but endangered cells encircling the initial damaged site. The wonder of the enhanced MRI technology, explains Steven Warach '88, assistant professor of neurology and radiology and director of the stroke division at Beth Israel Hospital, is that it illuminates this region and allows researchers to monitor how rapidly cell death is radiating outward.

Enter the second phase of this preventive strategy: a class of drugs being tried on stroke victims to break up the blood clots that travel to the brain to initiate a stroke. Blocked arteries, a condition that precipitates stroke, deprives the cells of blood, oxygen and glucose, which causes them to swell. Glutamate, one of the main neurotransmitters responsible for brain functions such as cognition and memory, builds up in the cell to poisonous levels. This event precipitates an influx of calcium, an overload that sets off another chain of events that eventually results in the breakdown of the cell membranes and cell death.

"Everything up to that point potentially can be reversed," says Warach.

"A whole hierarchy of drugs" in various stages of development and testing are currently being explored in clinical trials to test their effectiveness in protecting the ischemic penumbra. Nitroglycerine and nimodipine have proven effective in animals in protecting the brain from damage due to stroke. A trial beginning in January 1995 will look at a drug called ancrod, a derivative of snake venom, which may help if taken in the first three hours.

A class of drugs being referred to as "lazaroids"—after the biblical Lazarus

who rose from the dead—are also being administered to halt neural damage. Calcium binds to calmodulin, a partnership that activates a chain reaction resulting in the release of free radicals. Set loose, these highly reactive molecules assail cell membranes to break them down. Lazaroids target the free radicals, while another drug called citicoline works as a substrate to strengthen and stablize the membranes. Currently, lazaroids and citicoline are being tested separately in clinical trials, but Warach suggests that multiple drugs may be administered together in the future.

Stuart Lipton, associate professor of neurology at Children's Hospital, is investigating the complex role of glutamate in neural damage, including stroke, but also other diseases such as AIDS-related dementia and Alzheimer's disease. He has been conducting research on the drugs Cerestat and the German drug memantine, which has been used in that country for a number of years to treat Parkinson's disease and influenza. Animal studies show that these drugs are effective in blocking the NMDA-receptor-activated channel, one of two main types of glutamate receptors in the brain, which is responsible for regulating calcium levels in the brain. Clinical trials are under way that will test these drugs to treat stroke, Lou Gehrig's disease, neuropathic pain and AIDS dementia.

As revolutionary as this research is, says Warach, it all depends on the patient and the patient's physician. Too many people come to him "grasping at hope," he says, but they come too late. "After a day or so, the damage is done and irreversible."

Warach stresses thinking of a "brain attack" as analogous to a heart attack, and emphasizes that people need to respond as immediately to symptoms of stroke just as they would to an myocardial infarction. "We have to change the way of thinking of patients and doctors," he says. "There are things that can be done."

*Terri L. Rutter*

**Migraines Under Observation**

Building on pivotal findings about the cause of pain in migraine headaches, professor of neurology Michael Moskowitz and his MGH team are now trying to record what happens in the brain during onset of an attack.

He is recruiting migraine patients who are instructed to call the lab as soon as they get any warning of an attack; most often this is a pre-migraine aura—a visual hallucination that temporarily obscures the vision. Patients come in for an MRI scan within 30 minutes for observation. In addition to being placed in the scanner, patients are interviewed about any environmental circumstances that may have lead to the attack. One of Moskowitz's best subjects thus far is his associate, F. Michael Cutrer, an instructor of neurology. Moskowitz and Cutrer, along with Bruce Rosen, director of clinical MRI at MGH, are using the MRI scanner to observe and record what takes place in the brain during the onset of a migraine attack. This project is being funded by a grant from Glaxo Pharmaceuticals.

This work grew out of earlier research that indicated that the throbbing pain of migraine is not due to an increased blood flow to the blood vessels in the brain, as has been believed but unsubstantiated for the past sixty years, but by nerve terminals that are temporarily hypersensitized to blood flow by the release of peptides. As reported in 1993 in the *Journal of Neuroscience*, Moskowitz's team found that exisiting migraine drugs work by blocking pain signals from the trigeminal neuron, not because they constrict cranial blood vessels. This finding, if replicated by other researchers, could lead to the development of a new class of anti-migraine medications. There is a great need for new drugs because while current medications, such as sumatriptan and ergot alkaloids, effectively stop migraine pain, they also constrict blood vessels and are therefore unsafe for those patients who also suffer from hypertension and heart disease.

While Moskowitz's work has shown that the peptide release is responsible for migraine pain, he has not yet determined precisely what causes this release. Among other tasks, scientists must sort environmental triggers (such as anxiety or physical stress) from internal chemical triggers.

One of the essential questions, says Moskowitz, is "What triggers migraine pain?...Individuals have different kinds of pain. How do these relate to the pattern of pain that develops?" He is hoping that the MRI research will answer these questions and lead to the development of new therapies.

*Sarah Jane Nelson*

# How the Neuroscien

*by Philip R. Sullivan*

DISCOVERING THE SECRETS OF ATOMIC power, penetrating the mists of our early universe, and unraveling the double helix of DNA represent such dazzling twentieth century accomplishments that, at times, our human abilities to penetrate nature's secrets seem boundless. Nevertheless, neuroscientists remain concerned that the human brain may be more complicated than it is smart, in which case we will never be able to lay bare its full workings. Despite this possibility, scientists during the present decade of the brain have learned enough to cast doubt on previous postulations.

Much of the initial research focused on the edges of the nervous system, a sensible strategy since its periphery is more accessible. But neuroscientists continued then to trace the paths of transmission and refinement of data ever more deeply into the brain's hidden recesses. As investigation progressed from level to level, a rather fuzzy expectation existed that—to provide an illustration from the much studied visual system—the data initially culled from the environment would eventually all come together for final viewing within some higher center, some TV room of the mind.

So let's for a moment pursue that analogy. Electromagnetic radiation first impinges on the TV's antenna. Suitable connections deliver this information to the set's innards where it is further processed and eventually converted into an electron flow that is targeted onto a coated screen. There it all comes together for our viewing. In similar fashion, electromagnetic radiation touches our eyes. Suitable connections deliver the initially processed information to our nervous system's innards, where it also becomes converted eventually into an "image" suitable for viewing.

# tist Lost His Soul

Unfortunately, this analogy works poorly. It's all well and good, for example, to think of an orderly sequencing of information, taking one logical step at a time as our TV set does on its way to the finished picture; but our brains just don't function in that relatively simple, linear fashion. In actual fact, various elements of visual data are processed simultaneously in multiple brain areas, and there is no one place where it all comes together for our viewing. (Even in the simpler macaque brain, there are 32 separate cortical areas involved, often processing data in parallel and interconnected by at least 305 distinct tracts.)

And there's a still worse problem, which can be hammered home by further comparison with the operation of our television sets. Advertisers, after all, are not happy when we turn on our monitor and walk out to the kitchen. In order to fulfill its purpose, the TV requires a viewer, and that viewer is outside the set. It's obvious that I'm the one who views the completed work of my television receiver. But, even if there had been a single place in the brain where it all came together for viewing, *who* in the world would be there to look at the completed work?

To answer this question, most of the traditional theories had resorted to one or another theory of "substance dualism," referring to two-joined-entities whose interaction was to account for our human awareness and behavior. One of the entities, our body, is quite obvious; it is extended in space and directly discernible to all five senses.

The other entity, however, has always seemed rather mysterious. This elusive whatever-it-is had been given the job of explaining our aliveness and our consciousness. Since the proposed entity slipped away with our final

breath, and since the old Latin word for breath was "anima," it was often referred to by this term, usually translated into English as spirit or soul.

One common version of this entity, going back to the ancient world, going on to the Shakespearean era (e.g., Hamlet's ghostly father), and still going like an Energizer battery up to the present time, consists of a gossamer substance that is sometimes translucently visible and that takes the same shape as the physical body it *anima*tes. This "astral body" (in New Age terminology) is ideal for movies (e.g., *Ghost*) because you can see it rising from its almost identical physical body after sloughing off its mortal shell. And though this "astral body" (or some even more subtle "spiritual substance") would have problems viewing the visual "image" produced by the brain—since there is no one area analogous to the TV screen—it would at least answer the question: "*Who* is viewing the picture?"

In fact, one might well argue that a scientifically baptized entity of this sort would be less bizarre than the *up* and *down* and *strange* and *charm* quarks that particle physicists tell us about with their faces almost straight. Unfortunately, however, the positing of a dualist explanation for our mental life caused, from the cognitive scientist's perspective, more problems than it solved. Here's why:

Starting with our TV analogy, we can make a separation into computational system and viewer outside that system. Now we apply this model to ourselves and make a separation into computational system (brain) and viewer (astral body or soul substance) outside that system. Having assumed this way of thinking, we must be logically consistent in its application. So let's state our adopted way of thinking as an axiom: A viewer must always be outside the system which is to be viewed.

Applying this axiom to our own case presents no problem at all for substance dualism. No problem, that is, the first time around. Who views the image elaborated by our brain? Our astral body, say. But, then, who views the image elaborated by our astral body? And then, who views the image elaborated by whatever entity views the workings of the astral body… and so on indefinitely. We are into a logical morass created by an infinite regression of viewers.

*"The positing of a dualist explanation for our mental life caused more problems than it solved."*

Perhaps the astral body enthusiast might want to answer: "No one has to view the doings of my astral body from outside. My astral body does the final viewing, and that's all there is to it!" But if we are not going to demand that our axiom be followed every step of the way—A viewer must always be outside the system which is to be viewed —then let's drop it at the very first step rather than applying it inconsistently; that is, by requiring it at the level of brain function and then dropping it at our convenience once we've postulated a new entity (which had been created in the first place in order to remain consistent with our axiom).

Cognitive scientists concluded, once they'd focused on the issue, that our intuitive liking of the "outside the system" axiom comes from the fact that, in our everyday experience, we are outside all the physical objects we view (i.e., literally see). However, such an axiom has no strict, logical necessity. A simpler hypothesis, roughly stated, is: Consciousness proceeds from brain function as motion proceeds from muscle function.

Traditional philosophers could point out, however, that their subtle concept of spiritual substance avoids the logical problem of infinite regress, and for this reason: material substance of its very nature is extended in space, but Descartes' '*res cogitans* (thinking thing) has no parts and no extension in space. Its presence can be inferred, though, from such activities as our use of abstract terms that have no physical dimensions (e.g., the concept of "concept").

The next point in their reasoning is a bit tricky, but it goes like this: material objects could never reflect back completely on themselves as we do in states of self-consciousness because extended parts would, at some point, get in the way of each other. But an "immaterial substance," having no parts and no extension in space, can readily reflect on itself because there are no parts to get in the way. Spiritual substances, therefore, are exempt from the general rule that an observer must be outside the system observed. The morass of an infinite regression of viewers is thus avoided. And there is a happy dividend, a joyful spinoff, attached to this "thinking thing."

Because a spiritual substance is not extended in space, because it therefore has no parts, there is nothing in it that can be taken apart, which is after all how material objects are destroyed. Therefore, this spiritual substance is naturally immortal. We will continue to live, even though our bodies die! (And, indeed, this ever-lastingness of each human being was seen as underlying the unique dignity of the human race.)

But having saved themselves from the intractable problem of infinite regress—and at the same time having frosted our cake with the rapturous notion of personal immortality as a natural aspect of being human—traditionalists came hard upon another problem. If the presence of consciousness is to be explained by a proposed spiritual substance, how are we to account for the presence of consciousness in other animals? Unless, that is,

we are going to gift them with a similar substance to underwrite their consciousness, in effect, a soul substance that would bestow upon them the same immortal dignity as the human race.

After pondering this problem, René Descartes came up with the following solution: the other animals are in fact *not* conscious; they are merely complex machines whose very intricateness of response creates in us an illusion of consciousness. Needless to say, this explanation was not highly contagious.

In any case, that particular issue was merely an opening hurdle for substance dualism. For if we are composed of two totally different things (sometimes referred to by Scholastics as "incomplete substances" since they are naturally conjoined), how are these totally different substances, matter and spirit, to interact causally? After all, physical objects can literally push and pull each other around, or they can influence each other through one or another form of physical energy, as when I literally shine light on a subject with my flashlight. Spiritual substance, by contrast, has no extension in space, no mass, and no physically detectable energy.

The best solution that even the brilliant Descartes could devise was a fantasy in which his thinking thing interacted with the brain through the unpaired pineal gland, a proposal that, aside from its neuroanatomical implausibility, completely side-stepped the basic issue of how two such radically different substances were to interact in the first place.

Finally, it is the total dependence of consciousness on a functioning brain that creates the biggest stumbling block for substance dualism. Destroy a small area in the brain stem (reticular activating system) and consciousness is permanently lost. Destroy an area of the left cerebral hemisphere ordinarily supplied with food and oxygen by the middle cerebral artery and all verbal consciousness is lost. And while we could continue to document at great length, via additional examples of brain pathology, the total dependence of consciousness and its various shadings on the functioning nervous system, such an excursion is not really necessary since we experience that dependence during the course of every night. As part of our normal 24-hour cycle, the brain alters its pattern of activity in deep sleep; and during these periods, we have no consciousness at all. We are, as the saying goes, "dead to the world." Now, if we are going to posit a separate soul-substance to explain consciousness, why is this "thinking thing" not doing its proposed job whatever the brain may be up to at the time?

*"A theory that so facilely explains everything explains nothing."*

The dualist diehard can of course come up with an ad hoc addendum to his theory, such as: the spiritual substance has to interact with the material substance of the body in order to bring about consciousness, just as I have to interact with my car if I'm to drive cross-country. But this amended theory was still found wanting, because a proposed substance that cannot even account for its own central activity without a functioning brain added nothing significant to an account of consciousness based on the functioning of the brain itself.

Indeed, worse than being simply of no help, this proposed entity had a tendency to short-circuit progress in cognitive and neuroscience because it seemed at first glance to provide a ready answer for almost any question asked. What accounts for my being conscious rather than not conscious? My thinking thing. What causes my attention to be focused now on this, now on that? My thinking thing. What allows me to recognize the correct name from those proffered by my brain's memory file? My thinking thing. And on and on. But a theory that so facilely explains everything explains nothing.

And so it came to pass that neuroscientists stopped thinking in terms of two different substances, the body and some additional entity. Instead, they began to look at consciousness as simply a natural manifestation of brain function...and that, in a nutshell, is the story of how the neuroscientist lost his soul.

But, of course, the story doesn't fully end there, because the implications of any theory tend to spread beyond the borders of its immediate purview, sometimes creating external resistance to its acceptance. The Copernican theory that displaced earth from the center of our universe, the theory of evolution by natural selection, and Freud's theory of unconscious mental activity, each were seen at one time as incompatible with the traditional Western faiths, but no longer so. Similarly, one need not postulate a naturally immortal soul substance in order to believe, say, in the Christian doctrine of Resurrection; though theologians have some work to do if their dualist religious teachings are not to seem as quaintly unbelievable to the next generation as Creation in Seven Days does to the educated person of our present age.

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Personality Photos Inc.

**Jack Nicholson joins other "mental patients" in this scene from *One Flew Over the Cuckoo's Nest.***

# Is Psychiatry

*by Joseph T. Coyle*

# Dead?

In popular culture, the psychiatrist has often been viewed as a middle-aged, bearded, white man dressed in a suit, sitting in his office treating patients by means of "talking therapy." A less common figure is the white-coated, aloof, authoritarian physician, who uses physical restraints and medications to subdue severely disturbed patients in the mental hospital. The former is regularly the subject of *New Yorker* cartoons and the latter has its roots in Ken Kesey's *One Flew Over the Cuckoo's Nest*. These two caricatures are also symptomatic of a rift between psychodynamic psychiatrists and biologic psychiatrists that has sundered the field in the past.

Fortunately, the basis for these two distortions of the practice of psychiatry is in its agonal stages; we need not mourn its imminent demise. Traditional psychiatry was done in by two implacable forces—scientific advances and the reorganization of health care. These two forces have so radically changed the fundamental understandings of the causes and methods of the treatment of mental disorders that the transformation is akin to a paradigm shift. What are the elements that forced these changes?

The first major change was brought about 20 years ago by an interest in developing an empirically grounded diagnostic system, known as the Diagnostic Statistical Manual or DSM III. Previously, psychiatric diagnosis was largely descriptive and relied upon inferences about unconscious conflicts. By exploiting the methods of epidemiology, the science of disease classification, a diagnostic framework was developed that, just like general medicine, relied on objective signs and symptoms. This permitted reliable diagnoses, which predicted the course of illness and treatment response. Over the years, diagnostic precision and reliability have been improved by scientific refinements, which have led to the DSM IV.

Armed with an effective diagnostic instrument, researchers were thus able to determine the prevalence of mental and substance abuse disorders in our society. Studies have unmasked the secret but enormously costly epidemic that has been hidden by stigma. Severe, disabling mental disorders impair 8 to 10 percent of our population at the present time; disabling substance abuse affects another 8 percent of the population. One in four Americans will experience a significant psychiatric or substance abuse disorder at some point in his or her life.

In aggregate, our nation's direct medical care costs and indirect costs (e.g., productivity losses) from alcohol, drug abuse and mental illnesses totaled more than $300 billion in 1990, far exceeding the costs for cancer, AIDS or coronary artery disease. Furthermore, epidemiologic studies revealed that fewer than half of the patients suffering from severe disorders such as major depression are appropriately diagnosed and adequately treated.

The second major advance has been the growth in brain research over the last quarter of a century. Progress has been so dramatic that approximately 90 percent of our current knowledge about the brain was acquired in the last decade. The Society for Neuroscience, the main scientific organization for those involved in brain research, was founded 25 years ago with a few hundred members; now 25,000 scientists and doctoral candidates are members. This discipline ranges broadly in its ken including regulation of gene expression in the brain, mechanisms controlling the development of the brain and the organization of neuronal networks into functional systems.

A striking principle that has emerged from this research is that the brain and its functions are shaped by an interplay of biologic, psychologic and social factors. This knowledge has figured importantly in the development of more powerful insights into the determinants of mental disorders.

One of the compelling links between the brain and mental disor-

ders was the discovery that certain drugs were effective in the treatment of severe mental disorders including schizophrenia, depression, manic-depressive illness and anxiety disorders. While the early years of psychotropic drug development relied on serendipity, (i.e., chance discovery), recent advances in neuroscience have heralded a new era of rationale drug design that has led to agents with much more specific therapeutic effects and fewer side effects. For example, fluoxetine, a specific potentiator for serotonin, was developed to clearly target this neurohormonal substance. It is effective in severe depression as well as in obsessive compulsive disorder, but is free of the cardiotoxic side effects associated with the "first generation" of antidepressants.

The molecular targets for drug action have been clarified through an increasing understanding of the dysfunctional neuronal systems responsible for mental disorders gleaned from studies of post-mortem brains obtained from patients with specific disorders. This knowledge holds the promise for the development of new, more effective treatments that exploit novel mechanisms closer to the causes of disabling mental disorders.

*"The human brain is now much more accessible to research because of recent developments in imaging techniques."*

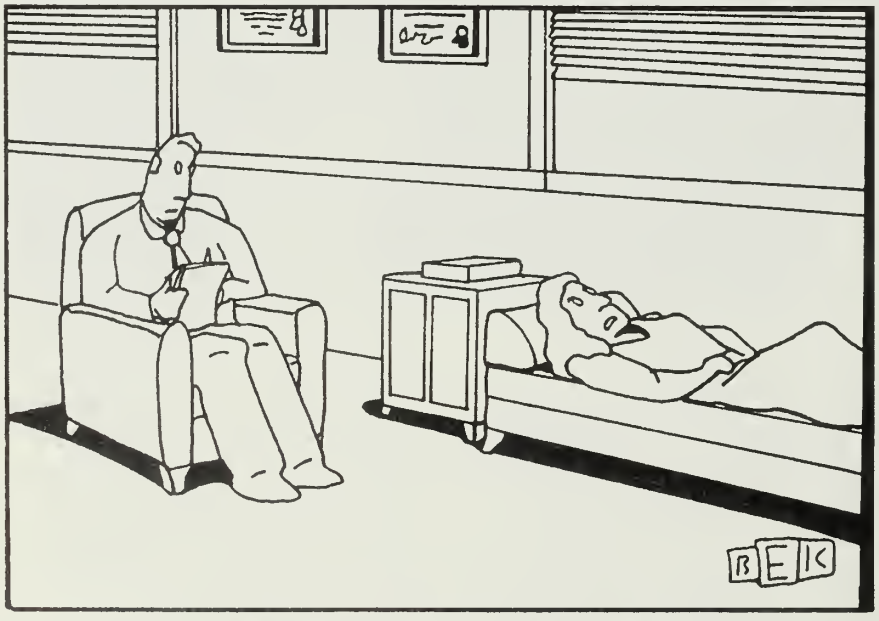
The human brain is now much more accessible to research because of recent developments in imaging techniques, which permit visualization of the structural anatomy, chemistry and regional neuronal activity of the brain in living subjects. These methods have begun to elucidate the neuronal systems and their functions that correlate with specific cognitive tasks. This recent research renders moot old debates about the distinction between mind and brain and has led to a growing consensus that the brain is the organ of the mind.

Brain imaging methods have transformed fundamental concepts about the cause of many mental disorders, which previously had been ascribed to unconscious conflicts. For example, computer assisted tomographic (CAT) scans have revealed consistent reductions in the volume of the cerebral cortex in patients afflicted with schizophrenia; and nuclear magnetic resonance (NMR) scans have shown that atrophy of specific cortical regions correlates with the severity of such symptoms as hallucinations and disordered thinking in individual patients. In contrast to normal individuals, the inability to activate the frontal cortex when challenged with specific mental tasks is also a consistent finding in schizophrenia. These structural and functional abnormalities have been linked to neurochemical changes found in studies of the brains from schizophrenic patients after death.

Functional brain imaging has disclosed an area of neuronal hyperactivity in the left frontal part of the brain in patients with panic disorder. Furthermore, patients with panic disorder, who respond to an effective pharmacologic treatment or to an effective psychologic treatment, exhibit comparable reductions in this abnormal neuronal activity. These findings effectively derail the artificial distinction between psychological and pharmacologic treatments—both exert their therapeutic effects by correcting the dysfunction of neuronal systems in the brain.

Situation-dependent psychopathology has also yielded to brain imaging. Obsessive compulsive disorder (OCD) patients are often immobilized by fears of contamination. Presentation of a feared object to an OCD patient causes marked activation of neuronal pathways in the medial frontal cortex, the very part of the brain that has been the target of the frontal lobotomy.

Recovered addicts develop intense feelings of craving when placed in social situations associated with their




Drawing by Bruce E. Kaplan; © 1994 The New Yorker Magazine

*"Well, I do have this recurring dream that one day I might see some results."*

previous addiction. Craving appears to be an important contributor to relapse. Imaging studies have shown that recovered cocaine addicts, when presented with drug paraphernalia, experience craving in association with the activation of the amygdala, a brain structure responsible for the sensation of pleasure and anxiety. This discovery foreshadows opportunities for reducing the risk of relapse, based not simply on addressing "moral weakness" but on the underlying brain mechanisms.

This focus on the neurobiologic underpinnings of mental and substance abuse disorders might be misinterpreted as justifying only pharmacologic treatments. To the contrary, psychological interventions are thriving and expanding as their application is refined through empirical studies of efficacy. Compelling results from controlled trials have demonstrated the efficacy of cognitive therapy in certain forms of moderate depression, of behavioral therapy that employs systematic desensitization in panic disorder, and of problem-oriented brief psychotherapy in correcting maladaptive behavior and anxiety. Equally important is the evidence that psychotherapy in conjunction with antidepressant treatment hastens recovery and reduces relapse in patients suffering from severe depression. Family therapy can reduce relapse rate and the total dose of antipsychotic drugs in patients suffering from schizophrenia.

With the reorganization of health care, the growth of managed care and the advances in psychiatric diagnosis and treatment, the way in which psychiatric care is now provided has changed more dramatically than in any other medical specialty. Previously, mental health care was provided either in mental hospitals or in regular visits to a psychiatrist's office with little communication between the two. Hospital stays were long (weeks to months) with a goal of restoring of the patient to hoped-for normality before discharge.

Some studies indicate that long hospitalization interferes with the patient's ability to resume normal activities and responsibilities of life. Increasingly, mental health care is organized around a continuum of treatment with patients moving to less restricted treatment settings as symptom resolution permits. These treatment settings include day hospitals, supervised residential care and intense outpatient treatment programs, with close communication across these levels of care. Rehabilitation, especially for severe disorders, is now emphasized. As a consequence, the length of stay in psychiatric hospitals has plummeted as less expensive and less restrictive forms of care have grown in their place. For example, in a period of six years, the average length of hospitalization at the Harvard-affiliated McLean Hospital has decreased from 70 days to 13.

One might wonder whether the explosion in knowledge about the biologic underpinning of psychiatric illness and the increased emphasis on efficiency of treatment have dehumanized psychiatry and relegated care to simply writing prescriptions for psychotropic medications. This would be a misreading of the opportunities for improved treatment, which emphasizes a continuum across the biologic, psychologic and social determinants of mental illness.

The renaissance of psychiatry derives not from the claim that it has the answers for all the problems in society, but rather from the scientific reality that it has the methods to begin to understand and more effectively treat disabling mental disorders. In as much as the human brain and mind represent an approachable scientific frontier for rigorous study, psychiatry stands at the threshold for substantive advances of considerable benefit to society.

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# Phineas DisenGaged

What is rational? What makes it so? Our belief in ourselves as rational beings has empowered us to achieve a multitude of things. "I think therefore I am," said Descartes. But what about the other side of ourselves, the completely irrational feelings that we have? It is common knowledge that one cannot be logical if being emotional, and vice versa. Serious decisions are best made with a clear head, unclouded by emotion, or at least this is what we've always been taught.

From Descartes to Emerson to contemporary times, Western tradition has accepted that rational thinking is the stuff of hard science, while feelings, emotions and other touchy-feely states of being are the subjects of the "soft" sciences. Yet, because the brain houses the machinery that creates both thoughts and feelings, one might wonder if these seemingly oppositional energy waves don't run along beside each other once in a while. Recent neurological studies indicate that these two "divisions" may not be regimented to their opposite corners, but are interactive in a mutually dependent relationship.

Trying to understand how reason and emotion wrap, twist and unravel around each other is the job of Antonio R. Damasio, HW Van Allen Professor of Neurology and head of the Department of Neurology at the University of Iowa Hospitals and Clinics and author of the recently released *Descartes' Error: Emotion, Reason, and the Human Brain* (Putnam, 1994).

Damasio has spent 20 years investigating patients with severe neurological disorders. Among them was a man he calls Elliot, in whom a lesion in one part of his brain left him with the inability to feel feelings, while his rational thinking and problem-solving abilities remained intact. Elliot's lack of emotion, regardless of his rationality, however, led him to make entirely irrational decisions in his personal life, which resulted in tragic consequences. In other words, because he couldn't feel he couldn't think straight.

Experiences with patients with similar neurological disease inspired Damasio to wonder if reason and emotion needed to be reworked from Decartes's dualist configuration into one that reflected their interdependence. As he says in the introduction to *Descartes' Error:* "I began writing this book to propose that reason may not be as pure as most of us think it is or wish it were, that emotions and feelings may not be intruders in the bastion of reason at all: they may be enmeshed in its networks, for worse and for better."

This thinking led Damasio to test his hypothesis on comparable living patients and also on one of the most famous neurological patients of all time, Phineas Gage.

Gage's story is well known. He was a good man, well liked by his mid-nineteenth century compatriots. He was hardworking and destined for great things, according to his employer, the Rutland and Burlington Railroad in New England. One fateful day, while laying rail, Gage set off an explosion by tamping down on a mound of gunpowder with an iron rod. The blast sent the 109-cm long, 3-cm thick rod through Gage's face, skull and brain and into the air.

Amazingly, Gage survived this massive assault to his head. In the ensuing few months, however, his personality altered dramatically from the amiable, persevering person he had been to a belligerent, socially unacceptable fiend whose profanity was so extreme ladies were advised to avoid him. After a brieft stint as a freak in the P.T. Barnum circus company, he drifted away from society and died 12 years later in 1861, friendless and far from home.

Gage's story could have been banished to the annals of folklore if not for an enterprising young physician, John Harlow. Harlow was the first to treat Gage's wound, and the first to note his personality changes: "The equilibrium, or balance, between his intellectual faculties and animal propensities seems to have been destroyed," he wrote.

Two decades after the accident Harlow postulated that Gage's personality changes were due to damage to the frontal region of the brain, suggesting that the brain was divided somehow into different "parts" or "centers," which were responsible for different aspects of behavior. Harlow's theory, which he presented to the Massachusetts Medical Society, was ignored, however, because the prevailing thought at the time was that neurons were responsible for movement and language but did not serve any function in moral reasoning and social behavior. Harlow then requested that Gage's body be exhumed and the skull removed for examination. Since that time, the skull and the tamping iron that bore a hole in it—which was buried alongside Gage's casket—have been included in the collection at the Warren Anatomical Museum at Harvard Medical School.

While several postulations have been made over the past 150-plus years since Gage's accident about what caused his strange personality shift, just this year an answer may have been found. Damasio and his wife, Hanna (also a professor in the Department of Neurology at University of Iowa and an expert in neuroimaging), led a group of researchers who conducted a high-tech, state-of-the-art autoposy on Gage's skull. Using imaging techniques not even imaginable in Gage's time, Albert Galaburda, HMS professor of neurology and neuroscience, x-rayed the skull from all possible angles and rendered exact measurements of this famous head. "Today, thanks to imaging techniques, especially MRI, we can see details about brain structure where in the past this needed autopsy," says Galaburda.

Hanna Damasio then translated those figures into an impressive, three-dimensional image in a computer device she developed called Brainvox. Following this "reconstruction" of the skull, she fashioned a digitized version of the tamping iron, matching its exact dimensions, and then impaled the instrument through the computer image of Gage's skull. Although Gage himself only suffered this event one time, his computerized skull, in the comparatively safe virtual environment, was pierced several times, each thrust at a slightly different angle in order to

cover all the possible original trajectories. Finally narrowing it down to one pathway, the team was able to determine that the iron had knocked out portions of the frontal region of Gage's brain: the anterior half of the orbital frontal cortex, the polar and anterior mesial frontal cortices and the anterior-most sector of the anterior cingulate gyrus. Their study appeared in the May 20, 1994 issue of *Science*.

Gage's loss of brain matter in the frontal cortex corresponds to that lost by a small group of individuals who have exhibited similar behaviors: inability to make rational social decisions and to process emotion while maintaining logic and abstract thinking. The areas in the brain spared by flying objects or disease in these patients (whom Damasio draws together under one cognomen, "Gage matrix") were in the dorsolateral region, where the ability to do language and arithmetic originates. Gage-matrix patients, therefore, don't lose their capacities to play word games or complete multiplication tables because they haven't literally lost the brainpower that makes those things happen.

What they have lost is the ventromedial frontal region of their brains. Damasio has hypothesized that the terrain here hosts an "intersection" between rational thinking within the social domain and emotion. This region is wired to the amygdala, one of the gateways to emotion within the limbic system. Additionally, the number of a particular type of serotonin receptors in this region is high; experiments in monkeys have revealed that large doses of this particular neurotransmitter reduces aggression. Knock out the valise that holds this good mood-inducing elixir and, at least monkeys and most likely people too, experience very bad moods.

Damasio concludes that the brain systems damaged in Gage matrix patients are the very ones charged with processing goal-oriented decision making and reasoning and may also be involved in the development of emotion. He surmises then that emotion and rational thinking aren't developed in separate areas of the brain, but in fact are created together. This idea challenges the notion that higher brain systems create reason and wisdom while the lower brain operates the emotions. Or, as Damasio states: "Upstairs in the cortex there is reason and willpower, while downstairs in the subcortex there is emotion and all that weak, fleshy stuff."

Instead, Damasio argues, the neocortical region appears to be nonfunctional when the subcortical region becomes disabled, causing us to wonder if, as he concludes: "Nature appears to have built the apparatus of rationality not just on top of the apparatus of biological regulation, but also from it and with it. The mechanisms for behavior beyond drives and instincts use, I believe, both the upstairs and the downstairs." In other words, in order to feel straight, we must think.

Knowing that our thinking centers are connected, perhaps even dependent on, our emotion centers does not truly explain why we experience gut reactions: love at first sight, immediate repulsion, being stirred by a passion for food we rationally know we shouldn't eat, giving in to baser instincts. Should we completely ignore another adage from long ago: *carpe diem*? Is our mind/body playing tricks on us?

No, says Damasio. Because neurologists can understand within their laboratory walls why or how the brain creates an emotion, it doesn't lessen the impact of it: "...defining emotion and feeling as concrete, cognitively and neurally, does not diminish their loveliness or horror...." But now we know how to think about them.

*Terri L. Rutter*

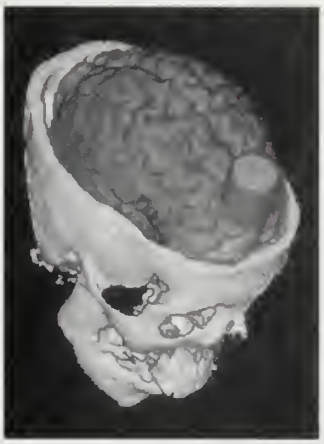


**Photo of Phineas Gage skull courtesy Rare Books, Countway Library. Brainvox images by Hanna Damasio, reprinted with permission from *Science*, "The Return of Phineas Gage: Clues About the Brain from the Skull of a Famous Patient" by Hanna Damasio, et. al., Vol. 264, 1102-1105, May 20, 1994. © American Association for the Advancement of Science.**


MADE IN U.S.A.

# The Addicted Brain

*by Steven E. Hyman*

MOST MEDICAL SCHOOLS TEACH THAT alcoholism and other addictions are diseases, but traditionally this classification of disorders has been based loosely on commonalties of onset, course and outcome, rather than on a theory of what is happening in the brain of the addicted person. Understanding how these substances can usurp people's self-control and—despite individual suffering, accidents and destruction of family—become the center of their lives is an important medical issue, which also raises significant questions about the normal functioning of the brain.

Given the pervasiveness and costs of addiction, it is troubling that usually capable physicians often fail to identify it and/or to intervene effectively if they do. This "blind spot" for addiction has been documented in many studies in both hospital and outpatient settings, and many reasons for it have been adduced. In some cases physicians are afraid of alienating valued patients; in others they are concerned that a diagnosis of addiction will be harmfully stigmatizing. Often, physicians are inappropriately pessimistic about the efficacy of treatment and treat relapses as absolute treatment failures, in contrast to other disorders in which relapses are understood to be an expectable feature of the illness.

To some extent the ambivalent attitudes of physicians toward addiction has also reflected the lack of a compelling pathophysiologic framework within which to understand the behavior of the addicted person. Progress in the neurobiology of addiction has been rapid in recent years and, while many details remain to be discovered, it is now possible to sketch an outline of the relevant pathophysiology with some confidence.

The reasons for such rapid progress are twofold. First, unlike other disorders that primarily affect thought, emotion and motivation, there are fairly good animal models of drug dependence, based on the fact that animals will self-administer drugs that produce addiction in humans. Second, advances in molecular biology have permitted the identification of all of the initial molecular targets of drugs of abuse during the past several years.

### Addiction as Disease

Despite the classification of addictive disorders, the idea that addiction—i.e., compulsive drug use despite negative consequences—represents a disease has been more a slogan or a weak heuristic than a compelling paradigm on which to base physician behavior.

The mechanisms by which compulsive behavior might be generated in the brain are certainly not intuitively

obvious using our usual method of thinking about behavior— introspection. After all, picking up a drink or lighting a cigarette are voluntary acts. Why can't the addicted person just stop this behavior after a serious physician warning or, even worse, after suffering some serious consequence of his or her habit, for example, an automobile accident, a bout of acute alcoholic hepatitis, or for the smoker, a myocardial infarction?

Physicians, like all human beings, may become frustrated and angry with individuals who do not stop drinking, smoking, or using drugs under such circumstances. It is very easy to see the strange behavior of the addicted person as nothing more than willful self-destruction. After witnessing several relapses of a challenging alcoholic patient, many a physician has wondered why society should be spending its scarce resources on such a person.

Scientific evidence that has accumulated over the last 10 years provides an antidote to such simple and counterproductive assumptions. At the heart of modern pathophysiologic models of addiction is the idea that in vulnerable individuals, the disease of addiction is produced by chronic administration of the drugs themselves, which cause long-lived molecular alterations in the signaling properties of nerve cells (neurons). In particular, drugs of abuse appear to commandeer circuits intimately involved in the control of emotion and motivation, thus impairing the insight and even the volition of the addicted person. At the same time, they produce nearly indelible emotional memories that predispose the person to drug craving and hence to relapse.

**The Neurobiologic Substrates of Addiction**

Two types of clues have led to the idea that opiates, cocaine (and related psychostimulant drugs), nicotine and ethyl alcohol, the most addictive drugs in widespread use, all tap into a brain system involved in the control of motivated behavior. The first set of clues followed directly from experiments first performed in the 1950s by Olds and Milner. They probed the brains of rats with a stimulating electrode and asked the simple question: are there locations of the electrode in the brain where a rat will work for electrical stimulation?

They discovered a small number of brain regions where a rat would press a lever tens of thousands of times in succession, ignoring normal needs for food, water and rest to gain electrical stimulation. In the popular literature these regions were called "the pleasure center" but scientifically they are better described as "brain reward regions," regions in which electrical activation is profoundly reinforcing.

A great deal of research since the 1950s has established that the most prominent substrate of brain reward is a pathway extending from the ventral tegmental area (VTA), an area of the midbrain, to the limbic system, the part of the brain primarily involved in emotion. With respect to brain reward, as opposed to other emotions, the most important limbic region innervated by the VTA is the nucleus accumbens (NAc). In the human brain the NAc is located where the caudate nucleus and the putamen come together in the ventral portion of the striatum.

The second set of clues concerning the neural substrates of addiction come from the drugs themselves. All of the classes of addictive drugs now troubling society were derived initially from natural plant products: opiates from the opium poppy, cocaine from the leaves of the coca plant, nicotine from tobacco, and ethyl alcohol from the fermentation of grain. Of the many tens of thousands of plant products that must have been sampled by human beings since the beginnings of civilization, many can affect emotions or alter consciousness, but it is the opiates, cocaine, nicotine and ethyl alcohol that have produced the highest rates of compulsive use.

We have learned in recent years that each of these highly addictive drugs mimic or enhance the actions of certain neurotransmitters (endogenous chemical substances in the brain that nerve cells use to communicate with each other). The opiates mimic endogenous opiate-like compounds called the endorphins; cocaine and related drugs enhance the actions of another neurotransmitter, dopamine; nicotine mimics the action of acetylcholine at its nicotinic receptors; and alcohol, among its many effects, facilitates the activation of a particular receptor for gamma-aminobutyric acid (GABA). While each of these four mimicked neurotransmitters has many diverse actions in the brain, they all share one common property: all affect the pathway extending from the VTA to the NAc that also serves as the substrate of brain reward with electrical stimulation.

The neurotransmitter released by VTA neurons on their targets, including the NAc, is dopamine. Experiments in which dopamine neurons are destroyed or in which dopamine receptors are blocked confirm that this neurotransmitter is required for brain reward. The psychostimulants, cocaine and amphetamine, both facilitate dopaminergic neurotransmission: cocaine by blocking the reuptake transporter protein that clears dopamine from synapses and amphetamine by causing its release.

Opiates are hypothesized to act on the brain reward circuitry by at least two mechanisms. There are opiate receptors on neurons in the limbic system, including the nucleus accumbens; thus opiates may act on these brain regions directly. There is now good evidence, however, that opiates can cause VTA neurons to release dopamine. VTA dopamine neurons are held in check by inhibitory interneurons. These interneurons, in turn, possess opiate receptors. Since opiates are themselves inhibitory, endogenous opiates (e.g., enkephalins) or opiate drugs (e.g., morphine) inhibit the inhibitory interneurons and thereby

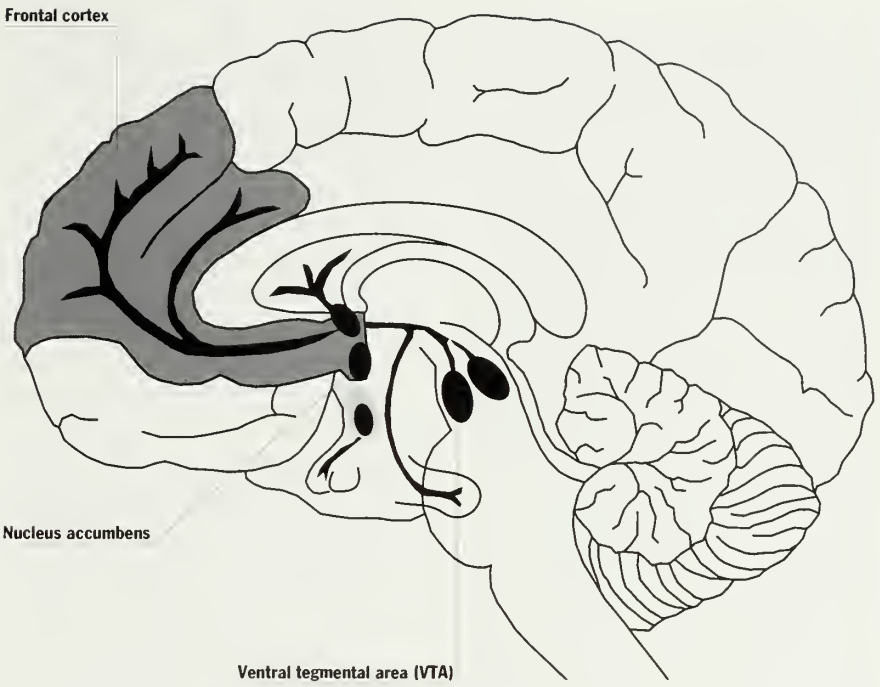
disinhibit the midbrain dopamine neurons.

The mechanisms by which ethyl alcohol or nicotine produce brain reward are less well established, but like the opiates, appear to cause dopamine release in this same circuit. Because drugs like cocaine or opiates stimulate this brain reward system with a longevity and power that does not occur with normally occurring, positively reinforcing stimuli, their motivational effects are profound indeed.

In addition to a drug's ability to tap into this brain reward pathway, several additional factors contribute to a drug's abuse potential. Drugs are most reinforcing when their level in the brain rises very rapidly; thus drugs that are smoked or injected produce far more powerful effects than drugs taken orally. It is an obvious, but important point that purer or more potent forms of drugs have more powerful effects on the brain. Purity and route of administration explain why cocaine smoked free base (volatilized pure drug exposed to the lung's massive surface area) is far more addictive than cocaine HCl absorbed via the nasal mucosa, which is in turn far more addictive than chewed coca leaves.

All addictive drugs have additional actions outside the mesolimbic brain reward circuit. The sum total of their actions in the brain determine their subjective and objective behavioral properties, and explain why opiates are sedating, for example, while cocaine is a powerful stimulant.

Why might we have a reward circuit in our brains at all? One simplistic but useful way to think about it is that some behaviors are too important to leave to the discretion of the cerebral cortex. If, for example, sexual behaviors were not profoundly rewarding, nature's experiment with sexual reproduction would have failed miserably. Rationally weighing the merits of sexual reproduction, absent some strongly motivating emotions, would clearly not have gotten the job done. Without limbic circuits that confer affective valences on different aspects of the world, and without circuits (like the mesolimbic brain reward pathway) that give values (and therefore priority) to certain behaviors, it is indeed hard to imagine how complex-behaving animals could survive.




**A sagittal section through the human brain showing the projection from the ventral tegmental area (in the midbrain) to the nucleus accumbens and the frontal cortex. Addictive drugs, such as cocaine, are thought to produce their rewarding actions by increasing dopamine in the nucleus accumbens and related limbic structures.**

At this point we might speculate that the mesolimbic brain reward circuitry was selected for in evolution as a mechanism to set certain behavioral priorities. By a kind of perverse serendipity, however, this circuit also makes our brains vulnerable to drug addiction because certain alkaloids and alcohols found in nature mimic or enhance the actions of neurotransmitters used within it.

### Transition to Addiction

The fact that certain drugs relieve dysphoria or even produce euphoria in humans, and are reinforcing in animal models, does not mean that they will produce addiction, i.e., compulsive use and inability to control use despite negative consequences. Indeed, over time the addicted person often has decreased enjoyment of his or her chosen substance because of tolerance. Despite diminished enjoyment, the life of the addicted person revolves around the obtaining, using and recovering from the effects of the chosen substance despite problems at home and at work, failure in life roles and often, increasing global distress. The substance is somehow so important that the addicted person is unwilling to imagine a day without it and may go to great lengths to deny that its use is causing any difficulty. The denial and often manipulativeness and dishonesty necessary to continue using the drug often frustrates and angers families and also physicians.

People who experiment with drugs or use them socially neither plan nor expect to become addicted. What happens in the transition from experimentation or social use to dependence? There is good evidence that use of a substance at adequate dose with adequate frequency and chronicity produces long-lived compensatory adaptations in brain functioning. These adaptations represent the

brain's homeostatic response to excessive bombardment by the drug or alcohol, and it is these molecular adaptations that produce addiction in vulnerable individuals.

It is important to recall, however, that not all people who use drugs become addicted. The majority of people who use alcohol do not become alcoholics; indeed for individuals who can use it in moderation, alcohol appears to have cardiovascular benefits and to enhance quality of life. Factors that make people vulnerable to alcoholism and drug addiction are complex. Speculatively we can divide these factors into two classes, those that tend to increase consumption (such as peer group behavior, drug availability and self-medication for distress), and those that might alter the threshold for addiction-related brain mechanisms to be affected by the drug.

These latter might include a person's genes, but events in a person's life are also important. It is significant, for example, that individuals with severe enough pain almost never become addicted to opiates even when they are used at high doses for long periods of time. When the pain ceases, there is usually no problem discontinuing the opiates. The analysis of what is known about factors that increase vulnerability to addiction deserves a separate extensive discussion. Here, I want to outline the kinds of brain mechanisms that likely produce addictive behaviors.

**Molecular Adaptations in the Brain**

Although all of the highly addictive drugs tap into the mesolimbic brain reward pathway, they are quite heterogenous with respect to their other sites of action in the brain. Specific syndromes of dependence and withdrawal depend on where in the brain receptors for each drug are found, and by implication, which particular brain pathways undergo long-term alterations in response to repeated drug exposure.

The types of long-term changes that addictive drugs produce in the brain can be divided conceptually into three categories. First, some but not all addictive drugs produce compensatory adaptations in brain regions that control somatic functions, thus producing physical dependence. Second, all addictive drugs appear to produce adaptations within the brain reward regions themselves. It is hypothesized that these are responsible for the motivational aspects of dependence and withdrawal and are critical to maintaining compulsive drug use. Finally, it appears that all highly addictive drugs produce profound positive emotional memories of drug use, which predispose the user to relapse, even long after detoxification, when he or she comes in contact with triggers or cues that are reminders of prior drug use.

These different types of long-term changes have varied time courses of onset and decay. Somatic withdrawal may last from days to one or two weeks; the motivational aspects of withdrawal may last from several weeks to months; emotional memories related to drug use may last a lifetime.

Of the highly addictive drugs, it is ethyl alcohol and the opiates that produce adaptations in brain regions that control somatic function. As a result, when a dependent individual discontinues one of these substances, a physical withdrawal syndrome occurs. In the case of the alcoholic, the well known withdrawal syndrome includes hypertension, tachycardia, tremor, nystagmus, insomnia and often grand mal seizures.

The most investigated somatic withdrawal syndrome, however, is opiate withdrawal. The noradrenergic locus coeruleus in the brain stem and related noradrenergic nuclei appear to be important final common pathway for this syndrome. Locus coeruleus neurons play a role in the control of autonomic function and other somatic functions related to the flight or fight response. Locus coeruleus neurons and some of their afferents have opiate receptors that respond to morphine-like drugs. Chronic bombardment of these opiate receptors with heroin, morphine or related drugs cause adaptations within the locus coeruleus and its inputs, which tend to compensate for the effects of opiates on the brain.

For example, molecules within locus coeruleus neurons that regulate firing rate increase in both amount and activity to counteract the chronic inhibition induced by opiate administration. When opiates are discontinued, these compensatory adaptations are left behind, causing locus coeruleus neurons to be hyperactive and thus contribute to the somatic symptoms and signs that characterize opiate withdrawal. These adaptations may take days to weeks to normalize, and as they do, the somatic aspects of the opiate withdrawal syndrome subside.

The discomfort of somatic withdrawal is feared by opiate addicts and may contribute to maintenance of opiate use. Nonetheless, it is not physical withdrawal, but what I have been calling the motivational aspects of withdrawal that are most important in maintaining the addictive state. Indeed, so highly addictive a drug as cocaine does not cause physical dependence or withdrawal at all.

What is meant by motivational aspects of withdrawal? The precise symptoms differ from drug to drug, but as users of addictive drugs emerge from an episode of use, even in the absence of somatic withdrawal symptoms, they may begin to experience a more or less severely dysphoric mood, inability to experience pleasure and, as time passes, increasingly intense drug craving. If the user has taken the drug or alcohol to relieve particular feelings of distress, the symptoms may seem magnified, markedly increasing craving for the drug as a means to relief.

Adaptations within the brain reward circuitry itself are thought to underlie these symptoms. Compared with somatic dependence on opiates, less is known about the precise mechanisms by which opiates, cocaine and other drugs produce such changes in

*"The voice of rationality is barely audible in comparison to the insistent demand for the drug."*

brain function. However, it increasingly appears that molecular compensations to overstimulation by dopamine in the NAc might be responsible for at least some of these aspects of dependence. Many alterations in important signaling molecules in both the VTA and NAc have been found to occur after the administration of opiates or cocaine-like drugs, both in animal models and even in studies of humans post-mortem. Moreover, noninvasive neuroimaging studies of humans suggests that there is significant functional impairment of regions of the brain receiving dopamine innervation during cocaine withdrawal.

The precise molecular changes that have been discovered in brain reward circuitry are complex, and will not be detailed here. Taken together, however, they suggest the hypothesis that addictive drugs, all of which increase dopamine action directly or indirectly, produce compensatory adaptations that tend to decrease dopamine effect within the system. Without the drug, this critical brain reward circuitry malfunctions.

In essence, a powerful system regulating motivated behavior and thus setting behavioral priorities has been commandeered by drugs. What the addicted person lacking his or her drug "knows" at some level is that another dose is required for them to "feel right," in essence to re-establish homeostasis. The voice of rationality (long-term best interest) is barely audible in the calculations of the addicted person's brain in comparison to the insistent demand for the drug.

A third and very important type of long-term change in the brain is not a compensatory adaptation, but a privileged type of long-term memory. There is increasing evidence to suggest that things learned during strong emotional states are more indelibly etched in our memories. Perhaps the most dramatic examples of emotional memory are seen in individuals suffering from post-traumatic stress disorder where even minor cues can bring the entire traumatic episode flooding back into consciousness. Among the huge welter of sensory inputs to which we are exposed each day, we can only attend to a small fraction and remember even less.

Our limbic system plays the key role in determining what is salient enough to attend to and to remember. The key to something demanding attention is its relevance to us. For example, circumstances in which individuals have experienced significant danger or profound pleasure are generally very well remembered, often with a great richness of detail. In contrast dry medical school lectures are often forgotten unless they provide information that we need to take care of a patient or unless the motivational device of an exam is looming.

The dopaminergic brain reward circuitry activated by drugs of abuse as well as dopaminergic, noradrenergic, and cholinergic projections elsewhere in the brain that are directly or indirectly activated by addictive drugs are likely to be involved in setting the strength of memories. Such mechanisms probably explain why even years after detoxification, individuals may experience profound craving and heightened risk of relapse if confronted by reminders of their former drug use. For example after a good meal, the former smoker may experience strong craving for a cigarette. The opiate addict driving by the neighborhood in which he used to purchase heroin may feel waves of intense craving and may even relive some subjective aspects of withdrawal. Of the three types of long-term change in the brain that characterize the disease of addiction, this type of long-term emotional memory is the longest lived; it may even last a lifetime.

In this essay I did not want to present the detailed data concerning drug-induced brain plasticity so much as create a framework to understand the pathophysiology of addiction. From this perspective we can understand the addicted person as someone whose ability to make appropriate behavioral choices is impaired by the way his or her brain functions. The idea that drugs of abuse may commander key motivational circuits in the brain helps us understand some of the otherwise irrational-appearing behavior of addicted people who continue to use drugs either openly or surreptitiously, despite a great deal of evidence that they are killing themselves and alienating all who are most important to them in their lives.

This model implies the importance of prevention, and underlines the fact that for those who are most vulnerable, recovery may never be complete because environmental cues can always engender intense cravings and risk of relapse. This model shows us we must redouble our efforts to strengthen the countervailing forces to those brain mechanisms that have been usurped.

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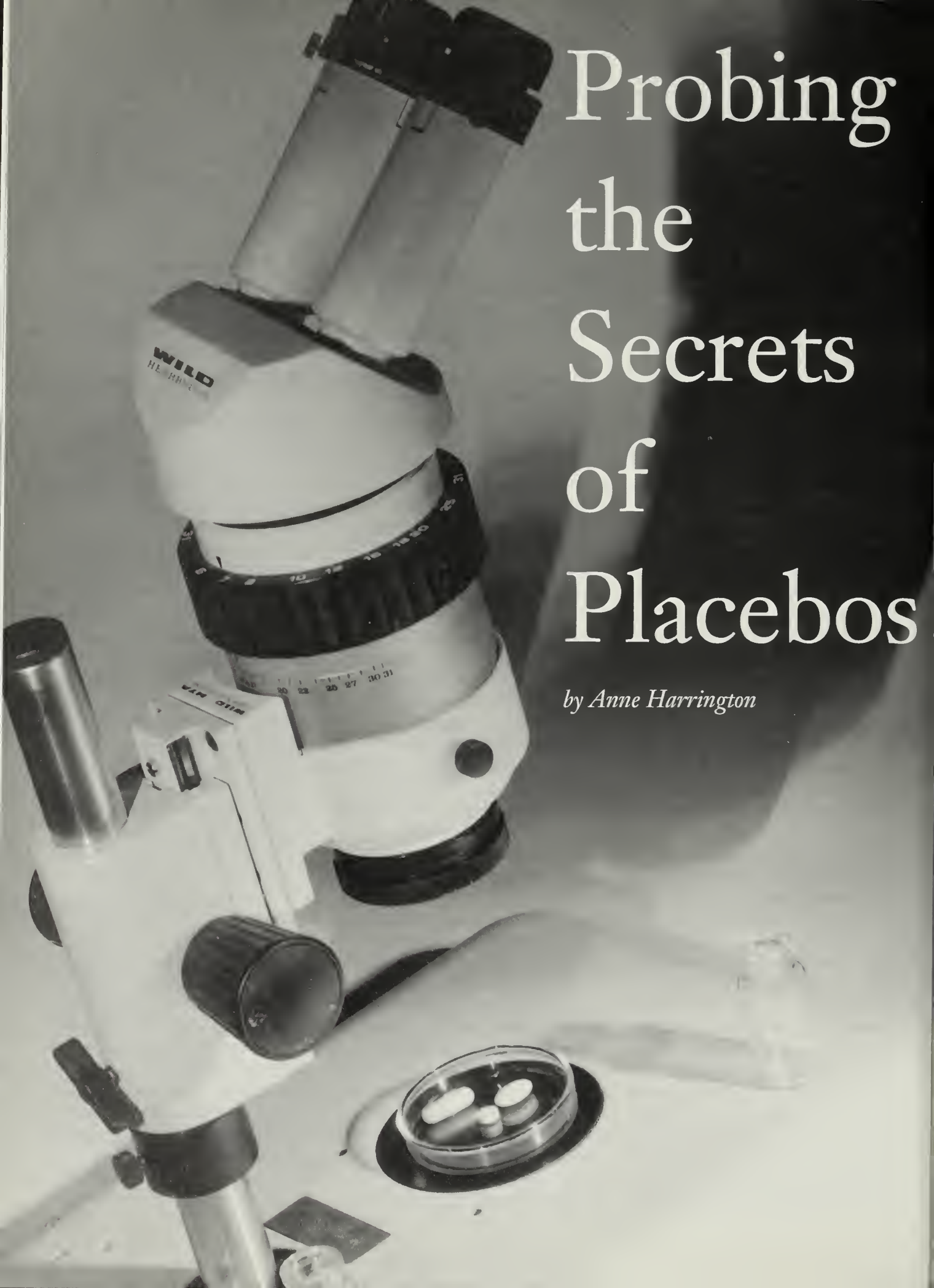


# Probing the Secrets of Placebos

*by Anne Harrington*

Mr. Wright, despite terminal cancer of the lymph nodes with tumors "the size of oranges," had not given up hope. Though he had ceased to respond to any conventional therapies, he had read in the newspaper about an experiemental drug called Krebiozen, from which he anticipated great things. When his hospital was chosen as an evaluation site for this drug, he begged to be included in the trials. Although Mr. Wright did not meet any of the criteria, his doctor reluctantly agreed and Mr. Wright received his first injection on Friday.

As described in a 1957 article by psychoanalyst Bruno Klapfer in the *Journal of Projective Techniques*, this is how his doctor described the scene on Monday morning:

*"I had left him febrile, gasping for air, completely bedridden. Now, here he was, walking around the ward, chatting happily with the nurses, and spreading his message of good cheer to any who would listen. Immediately I hastened to see the others who had received their first injection at the same time.*

*No change, or change for the worse was noted. Only in Mr. Wright was there brilliant improvement. The tumor masses had melted like snow balls on a hot stove, and in only these few days, they were half their original size!"*

The patient continued on this remarkable course until conflicting reports about the efficacy of Krebiozen appearing in the newspapers undermined his confidence and led to a relapse. At this stage, his physician, having determined that the "scientific interest of the situation" justified some duplicity, resolved to "play the quack." He gave Mr. Wright a new injection, not of Krebezion but merely of fresh water, and told him that he should not believe the newspapers, that his relapse was due to the fact that the original medication had decayed. This new batch, however, was fresh and extra potent.

*"Placebos are the ghosts that haunt our house of biomedical objectivity."*

The patient responded to this second intervention with an even more dramatic recovery. He returned home "the picture of health" and was symptom-free for two months. Then a final AMA announcement appeared in the press declaring Krebiozen "a worthless drug." Mr. Wright relapsed almost immediately, was readmitted to the hospital and died in less than two days.

The annals of medicine are filled with odd, high-drama cases like this, but they often so challenge our usual understanding about what kinds of healing are possible in certain situations that we just dismiss them as apocryphal (which some of them surely are), or let them stand as undigested curiosities. In fact, however, one could argue that the "miracle" stories of medical practice have special lessons that we would do well to reflect on. These are the stories that remind us—not subtly but with exclamation points—that no matter how sophisticated medicine may become technologically, a range of poorly-understood "other" factors may still sometimes swamp a clinical situation and send it scooting in directions that shouldn't happen.

In practice, of course, medicine has long acknowledged that "sham" treatments like fresh water injections have the capacity to rally endogenous healing processes within patients. This acknowledgment, however, has as often as not been marked by ambivalence and distaste. The very word we use to name the phenomenon at hand—"placebo response"—speaks to our ambivalence.

Placebo is Latin for "I shall please" (the opening phrase of the Catholic vespers for the dead, to which the word, ironically, originally referred). Placebos are therefore typically defined as sham treatments (bread pills, inert tonics, etc.) that physicians dole out merely to "please" or placate anxious or insatiable patients. Even when these physicians are convinced that impressive forces may be rallied through their maneuvers, they often cannot shake themselves free of the conviction that all this is at best unreal and at worst chicanery. Mr. Wright's physician was successful in giving a patient who lay at death's door two additional months of symptom-free living, but he still felt compelled to call himself a "quack" for doing so.

But the problems raised for medicine by placebo phenomena are not only ethical, they are also epistemological. In many ways, placebos are the ghosts that haunt our house of biomedical objectivity, the creatures that rise up from the dark and expose the paradoxes and fissures in our own self-created definitions of the "real" and "active" factors in our treatments. On the one hand, we acknowledge the power and ubiquity of placebo responses by our requirement that all new drugs be tested in double-blind placebo-controlled situations; however, we then define those same responses as the "nonspecific noise" in the treatment to be subtracted out of the picture. We often fail to notice that these factors are not inherently nonspecific, but only so because insufficient energy and attention has been spent on specifying them.

In 1969 the social psychologist W.J. McGuire described "three stages in the life of an artifact": first it is ignored, then it is controlled for its presumed contaminating effects, and finally it is studied as an important phenomenon in its own right. Currently placebo is still more often controlled away than studied, but one can track a thin trajectory of research literature that, from the 1950s up to our own time, has also attempted to

make the case for investigating placebo in its own right.

Tracking this literature as it has developed across time is an interesting exercise, not only because of the different kinds of information each study brings to an elucidation of the phenomenon, but also because each represents a distinct answer to the question of what a "science of placebo" should "look like." In fact, we do not just go out and investigate the placebo phenomenon: we constantly make decisions about what we think is important to know about it, and what kinds of explanations we are prepared to consider illuminating and rigorous.

Early clinical articles like Henry Beecher's "The Powerful Placebo" (1955) had been clear that placebos could cause "objective" (structurally and functionally measurable) changes in physiological functioning—some of which could even (one can imagine the words being uttered with a kind of hushed awe) "exceed those attributable to potent pharmacologic action." Nevertheless, even researchers who emphasized the physiological potency of placebos still seemed to suggest that explanations for that potency needed to be sought within some free-floating Cartesian mind space (often decked out with quasi-Freudian furniture) that possessed no clear means of "talking" with the body it was influencing in such useful ways. In a sense, the original decision to define placebo as the imaginary term in medicine's algebraic formula of treatment may have forced people's hand here: if an intervention that has been defined as unreal or inert turns out to work through biochemical or physiological mediators, then how could one continue to consider it "merely" a placebo?

Most of the early psychological explanations tended to focus on the patient. It was clear that not everyone responded to placebos. (A widely-cited statistic, going back to Beecher's 1955 study, held that 30 to 40 percent of any treated group responded to placebo; the figure was believed to be somewhat higher—about 55 percent—for pain relief). What kind of personality structure, then, responded to imaginary medications?

Often there was a quasi-pathological thrust to the attempts to answer this question, a vague undertone of condescension consistent with the general ambivalence most physicians felt towards placebos in general, and perhaps especially towards the patients who could be "fooled" by them. Using various standardized psychological tests and psychodynamic profiles, researchers thus explored the extent to which so-called "placebo reactors" might be unusually suggestible (or, alternatively, unusually hypnotizable), might have unstable reality-testing skills, might suffer from repression, hysterical tendencies or other neurotic symptoms, might exhibit unusual compliant, submissive personality traits, or might even be less intelligent overall than nonplacebo responders.

By the 1970s, however, no consistent "placebo responder" had been found, and such books as Jerome Frank's masterly 1973 *Persuasion and Healing* began to emphasize the

## To Hope Helps

**by Howard M. Spiro**

**As a gastroenterologist who gave up doing procedures about 25 years ago, I see many patients with complaints for which their doctors cannot, even after intensive study, find a reflection in x-ray or endoscopic image. Joining in lots of clinical control trials over the past decades, I was early astonished at how readily ulcer pain disappears, as quickly relieved by a placebo as by anything apparently more potent.**

**Pain and its relief, or at least its interpretation, have therefore become central to my professional life. I learned many years ago to realize how firm was the "right hand of fellowship" in the relief of pain and suffering.**

**I have used placebo therapy in what I hope has been an honest way. To relieve patients with symptoms out of proportion to objective findings, particularly those with pain whose source I do not immediately recognize and which I suspect will elude our categories, I have often suggested the injection of 1,000 mcg. of vitamin $B_{12}$. Customarily I have preceded this with something like: "These injections have helped many other patients. I cannot explain to you why they work and I cannot promise you that they will work. But many patients have told me that they feel better and stronger afterwards."**

**Over the years I have come to expect that my approach is labeled deception, and distinctions between "pure" and "impure" placebos are pointed out. In explanation—or expiation—to critics, I respond that $B_{12}$ as a placebo lessens anxiety and gives new strength from hope.**

**Physicians often use placebos without labeling them as such. The antibiotic for a common cold is well recognized and disguised, for relief of doctor and patient, as an "antiviral" agent. But many diagnostic studies and procedures are also placebos of a sort, designed to reassure by ruling out unlikely possibilities. Words can be placebos, and sometimes operations are, as well. But most commonly, placebos are pills; these are**

greater importance of immediate situational and interpersonal factors. Depending on the quality of the doctor/patient relationship, the nature of the "socially defined symbols of healing" used, or any number of other conditions, the same individual might be responsive to placebos or not. As early as the 1960s writers like Arthur Shapiro had reminded people that the physician was also important in the dyadic dance of healing and proposed that doctors—independent of what they did—were actually potent "placebos" in their own right.

He and others enumerated a number of specific variables that might endow some physicians with particularly curative mana: enthusiasm for treatment, apparent warm feelings for the patient, confidence and authority. Some gave this exercise an explicit psychoanalytic spin and proposed that the physician in a placebo-treatment situation acted as a parental "transference figure" on whom vulnerable patients projected childlike feelings of trust and submission along with expectations of being made better.

*"Placebo is still more often controlled away than studied."*

Others in these years began to dispute the substance behind some of the more fervent evangelical reports of miracle placebo cures and scoffed placebo effects as not involving real change in a patient's physical state at all. Instead, they said such cures simply represented a misattribution by the patient of various naturally-occurring and ambiguous changes in his or her clinical condition. Motivated to believe that he or she is being helped and wanting to please the physician, a patient will tend to downplay or censor his awareness of negative changes, will give undo weight to positive changes, and will then selectively attribute all welcomed alterations to the placebo drug. In a variation on this argument, others agreed that placebos did not change the supposed non-negotiable physiological realities inherent to a particular medical condition, but they proposed that placebo might ameliorate the distressing subjective concomitants of somatic illness, such as anxiety. (The subjective experience of pain, for example, is known to be intensified by anxiety.)

Then, in the late 1970s, two things happened in the brain sciences that seemed to raise the stakes considerably on the placebo question. The first of these was an outgrowth of the much-heralded discovery of certain naturally-occurring substances in the brain called endorphins. Chemically similar to opium-derived narcotics, endorphins attach themselves to the same receptor sites in the brain as morphine and thus appear to be the brain's own natural painkillers. In 1978 Jon D. Levine, N.C. Gordon and Howard L. Fields reported evidence that at least some forms of placebo analgesia were

**best given as a gift, as a symbol of loyalty, but too often they represent a challenge, to show patients that "it's all in your head," or even a ransom to get the unwilling patient out of the office.**

**Several years ago, fascinated by placebos, I began to look at what their benefit suggested about clinical practice and patient/physician relationships. That placebos help patients, that placebos help all of us, highlights some problems for me: 1. Disease, what doctors find, differs from illness, what patients feel—for placebos help illness far more than disease; 2. The molecular model of medicine is not sufficient to answer all our patients' needs; and 3. At a time when physicians regard themselves largely as conduits of power, purveyors of pills and procedures, the benefit from a placebo reaffirms the influence of the physician in the healing process, the miracle that to hope helps.**

**More recently (I trust that it is not senescence), I have been examining why "alternative" medicine has flourished over the past decade or so. "Alternative" medicine we doctors should really label "complementary," for it used to—and should once again—be part of our practice. Alternative practitioners spend a lot of time with their patients getting the "social history" to put the patient into context, a frame that helps them comfort the patient. The medications they dispense may not be as important as how such practitioners use them, and the benefits may come from catharsis as much as from anything more specific.**

**I find—you will forgive me—more than a few parallels in alternative medicine with psychosomatic medicine. In its heyday when I was at Harvard Medical School in the 1940s, psychosomatic medicine also taught us to see the person in the patient, to recognize mind and body, and maybe even spirit. Richard Cabot, of CPC fame, also left us that message in his book with Russell Dicks, *The Art of Ministering to the Sick*. Neurobiology brings a new reality to psychosomatic medicine as alternative medicine supplies its slightly distorted reflection. The help that a placebo brings tells me that doctors should not disdain alternative practices, but should learn from them.**

**Science, it is always important to confess, is still the basis of medical practice, but medical practice is stretched by the tensions between science, what can be measured, and intuition, what can be felt. Physicians need to regain confidence in the symbolic reality of medicine, the healing power of listening, and in the release of emotions that flow from the catharsis of words.**

**Hippocrates said, "For some patients, though conscious**

mediated by these same endogenous opioids. These researchers found that when patients receiving placebo medication for postoperative pain were given naloxone, a substance that blocks opiate receptors, the effects of placebo were inhibited.

Lively controversy ensued over both the meaning and consistency of the findings, especially when several other studies showed that naloxone could increase postoperative pain independently of placebo. In addition, it was pointed out that the data on endorphins also spoke only to the rather limited question of placebo analgesia and had nothing to say about the many other kinds of documented effects that had been associated with placebo interventions. And finally there were questions about just what kind of a finding the endorphin-placebo link really was: even if endorphins did mediate some kinds of placebo analgesia, that analgesia was not thereby explained (as some seemed to imply). Endorphin release, rather, became just one more placebo-generated phenomenon to be explained—and we remained as ignorant as ever about the processes whereby a person's belief in a sham treatment could send a message to his pituitary gland to release its own endogenous pharmaceutics.

Still, the discovery that endorphins might be involved in at least some forms of placebo analgesia (and the basic claim has held up) seemed so exciting on its own terms that there was a tendency to be relatively undeterred by the caveats and cautions of the gadflies. In fact, the intensity of the reaction suggests that the placebo-endorphin link came to mean something more than itself. It acted, not just as a set of findings, but as a notice to the hardheaded, physiologically-oriented members of the biomedical community that there were beasts worth hunting in this realm of human behavior after all; beasts who could be felled by the weapons experimentalists knew best how to use. Placebo, an "imaginary" treatment, had been found to have some solid flesh on its bones after all.

The second event that raised the biomedical stakes on the placebo question came in 1975. Robert Ader and his coworkers reported the results of a study with rats that involved a pairing (initially unintentional) of saccharin-flavored drinking water with injections of cyclophosphamide, an immunosuppressive and nausea-inducing drug. At this time, the immune system was believed to be a self-contained system not susceptible to influences from the central nervous system. Yet, when a subgroup of mice who were not given further injections continued to be fed drinks of saccharin water, they kept dying at a high rate. It seemed that the saccharin drink, because originally associated by the rats with the injections, now triggered the same immunosuppressive effects as the cyclophosphamide itself.

By "teaching" the rats to associate the saccharin water with the agency of the active substance, Ader had induced the immune systems of rats to behave in ways different from normal. In this

**that their condition is perilous, recover their health simply through their contentment with the goodness of the physician." Even so scrupulously scientific a modern clinician as Harvard's Bernard Lown, writing about the fabled Samuel Levine, has been astonished at the "lethal power of words."**

**Placebos have no power on their own. They are merely symbols, a seal to the contract between patient and physician. Prescribing a placebo is no substitute for time, energy or communication, but simply the promise of dedication. Giving a placebo is only the first step, a symbol of the physician's hope to help.**

**Placebos remind us doctors who feel so powerless, whipped as we are by managed care and ensnared by the diagnostic straitjacket of algorithms, that patients are people just like us. I would like to see placebos discussed in more than academic circles, for getting doctors to talk about such issues might illuminate our life and practice.**

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*"The imaginary treatment has been found to have some solid flesh on its bones after all."*

sense, he had created an experimental placebo whose effects on physiological functioning were incontrovertible. The fact that he had achieved this in rats rather than humans was a further blockbuster, because it undermined the frequent assumption that placebo effects were a product of peculiarly human interpersonal processes and unconscious wishes.

Actually, some researchers since the 1950s had tried to make the case that placebo effects were just a consequence of classical conditioning (or, in some formulations, of nonconscious associative learning processes). As Pavlov's dogs were conditioned to respond to an irrelevant stimulus (a bell) as if they were responding to meat, so individuals who have had successful trials with active medications (the unconditioned stimulus) become conditioned to respond to inert symbols of medicine (the conditioned stimulus) as if they were also active. This proposal, however, did not find a great deal of resonance until Ader's work helped put it on the front page of promising directions for unravelling the placebo problem.

Almost immediately, however, other voices continued to insist on the insufficiency of the paradigm, and to argue that the last word had not yet been said about the peculiarly human face of the placebo story. Social psychologist Irving Kirsch, for example, stressed that placebo-generated effects often followed a "logic of expectation" that was different from what would be expected if placebos merely evoked a conditioned reaction to some corresponding active agent.

The experiences of people who drink placebo alcohol are more closely linked to their culture's understanding of what it means to be "under the influence" than they are to the actual pharmacological action of real alcohol. In addition, there is evidence in the literature that the imagined effects of a substance can sometimes directly countermand its actual pharmacology. Back in 1973, Jerome Frank told of giving ipecac (an emetic) to a severely-nauseous pregnant woman and vigorously assuring her that this was medication that would help her. A balloon in her stomach showed that her stomach began contracting normally within minutes after "treatment."

To add a final layer of complication to the debates, a small cadre of medical anthropologists like Arthur Kleinman, Robert Hahn and David Moerman began in the 1980s to argue that nothing less than a broad sociocultural framework would do for making sense of the questions raised by placebo effects. Here placebo was conceptualized as a form of ritualized healing through symbols, and compared to the healing rituals practiced in societies across the world (practices that these societies in no sense consider to be imaginary or "sham," whatever the opinions of the Western world). The anthropologists asserted that symbolic healing is often quite effective, just as placebos are often effective, because human groups structure and partly create their experiences—including their bodily experiences—through shared symbols and metaphors. Thus Hahn and Kleinman wrote in the *Medical Anthropology Quarterly* in 1983:

*"Belief kills; belief heals. The beliefs held by persons in a society play a significant part in both disease causation and its remedy.... The significance of these beliefs in disease causation and cure is the same as that of microorganisms and medicinals: given certain conditions of host and environment, pathology of healing consistently follows belief. We describe these phenomena as 'culturogenic' or, more specifically, as 'ethnomedicogenic' disease and healing. Biomedicine, the predominant ethnomedicine of our society, participates equally in such causal practices."*

This final disciplinary reply to the question of what a science of placebo should "look like," not only cast the question in a larger framework than had previously been proposed, but also suggested that the hubris and ethnocentricity of Western high-tech medicine had blinded it to ways in which it still shared a common humanity with healing systems around the world. The moral message was clear: our most sophisticated pharmaceutical or surgical interventions actually share key formal properties with the bone-pointing or charismatic religious healing practices of groups we too often do not understand, let alone appreciate.

For better or worse—but certainly not surprisingly—few in the biomedical community have been very receptive to this message. Instead many continue to hope that placebo—if it cannot be ignored—will ultimately be demystified by a translation of its phenomenology into familiar physiological principles, a translation that will not require any destabilization or expansion of currently well-articulated modes of scientific investigation and understanding.

But how feasible—and even ultimately desirable—is this hope? My own view is that a total domestication of placebo into the language of biomedicine is in fact unlikely—but for this very reason it is such a fruitful problem for pushing our thinking and stretching our capacity for interdisciplinary cross-fertilization. If we listen and observe with care, we may find that this lowly phenomenon will start forcing us to ask why psychoanalysts, social psychologists, anthropologists, psychophysiologists and endocrinologists can all create compelling and internally-coherent stories about how

*"To understand the mind-body interactions of human beings, we must operate with a different logic altogether."*

and why placebo "works," but cannot figure out how to weave those stories together into a single explanatory narrative. Suddenly we are asking questions about the ways in which our culture organizes knowledge and has marked the joints at which reality must be carved and served out across the disciplines.

What kind of interdisciplinary intellectual demands does placebo make on us then? Here is a way that I have begun to conceive the larger challenges inherent in cracking open the "black box" of the lowly placebo: for many of us, it seems like the most natural thing in the world to talk about the processes of disease, physiology and healing as one "thing," and the sociocultural "context" in which those processes occur as another "thing." It is as if we imagined human beings to be little candy-coated pellets interacting inside some "space" but still maintaining a basic biological reality distinct from that "space." But does the placebo problem invite us to consider whether there is in fact no hard candy shell that rigorously separates our biology from our worlds of culture, belief and symbol? How possible is it that, instead of being candy-coated chocolate pellets, human beings are more like sponges? Sponges are animals who are saturated by the ambiance in which they live, and whose physiology presupposes the presence of that ambiance.

It would not make sense to speak of the physiology of sponges on the one hand, and the watery "context" in which they live on the other hand; the water is part of the internal works by which these animals function. Similarly, I suspect that our attempts to understand how the "context" of the clinical situation or the healing ritual affects the internal logic of our biology only end up confusing us in the end, because to understand the mind-body interactions of human beings, we must operate with a different logic altogether; a hybrid logic that asks us to insert the world of interpersonal relations, symbols of healing and intangibles like faith and hope directly into the body, and study the ways in which the entire system then functions.

We have hardly begun to think about how one might study the scope, limitations and conditions under which such a hybrid logic could be supposed to function, yet we also know that its products are ubiquitous in the world of medicine—and not only when physicians dispense sugar pills. In this sense, the problems raised by placebo effects have implications for clinical work in the broadest possible sense, and should be of the greatest interest to an interdisciplinary science of the human mind, brain and behavior committed to breaking down disciplinary divides in order to do fullest justice to its subject.

Placebo may have a dubious status in the clinic, but the fundamental questions it demands of us, pursued to their logical and most adventurous endpoints, promises to leave none of the disciplines involved in "cracking" its secrets unchanged.

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# The Malleability of Memory

No mere sum of computational parts, memory—the human brain's showcase of power—can in fact fade from the "pages" of our mind. Though amazingly accurate most of the time, memory may not only fade as information is forgotten, but can also be subject to change or distortion over time. "The output of human memory often differs—sometimes rather substantially—from the input," observes Harvard neuropsychologist Daniel L. Schacter.

Schacter, who has devoted the dozen years of his professional life to the scientific study of memory, has been continually aware of "the fragility of memory on one hand, and the power of memory on the other." Much of his work to date has been attempting to understand the different kinds of memory and their loci within the brain. In 1985 he and colleague Peter Graf were the first to differentiate two ways that memory is retrieved—what they termed explicit and implicit memory—which helped open the floodgates to the more sophisticated understanding of what is generally considered to be multiple, but separate, interacting systems of memory.

It is within this modern paradigm of memory that researchers can attempt to explain distortions of memory. Memory is not photographic; it is not like flipping back through pages of a book; it is not a linear computer-like process for storing, organizing and retrieving bits of information.

Memory, it seems, is more like a reconstruction. Different aspects of a memory are stored in scattered areas of the brain, linked in some way so it can be reassembled. Memories are superimposed on one another. Thus, the retrieval of the memory of one event, it is postulated, can be influenced by part of other memories that might also get activated.

Your emotional state at the time you're remembering—severe stress or depression, for example—can influence what you recall. And you can remember something, but forget the source of that memory; you may think it really happened, but it may have been a dream or something you read or were told.

"Memory is malleable in the sense that there are conditions under which it can be distorted," says Schacter. "And even if not historically accurate, it can still have a powerful effect on beliefs." Much is at stake in illuminating the neurological basis of memory distortion—a term nearly synonymous with the more charged phrase "false memories"—because of the debate over the accuracy of recovered or repressed memories of childhood abuse. Memory distortion seemed ripe for an interdisciplinary focus and thus became the subject of the first conference of the Harvard University Mind/Brain/Behavior interfaculty initiative. Schacter, who is a professor of psychology on Harvard's Faculty of Arts and Sciences, chaired the organizing committee, which brought together cognitive psychologists, psychiatrists, neurobiologists and social historians for three days in May 1994. Discussions of what is known about memory provided a foundation for understanding memory distortion and underlined the need for more study.

Schacter's own contributions to knowledge about memory come from cognitive neuroscience, an effort to understand the relation between the brain and such forms of cognition as memory, perception, language and problem-solving. In this approach to learning about memory, he uses studies of patients with memory disorders that result from brain lesions—such as amnesics—and neuroimaging techniques, such as positron emission tomography (PET).

Amnesic syndrome—which can occur as a result of stroke, brain tumor or encephalitis—is probably the most extensively studied neurological disorder of memory, says Schacter. (This is not the hit-on-the-head kind of temporary amnesia often portrayed in

**"Commitment" by Ben Freeman; 66" x 72"; mixed media, 1992. This is part of Daniel Schacter and Susan McGlynn's collection of memory-related art.**

*When from a long-distant past nothing subsists, after the people are dead, after the things are broken and scattered, still, alone, more fragile, but with more vitality, more unsubstantial, more persistent, more faithful, the smell and taste of things remain poised a long time, like souls, ready to remind us, waiting and hoping for their moment, amid the ruins of all the rest; and bear unfaltering, in the tiny and almost impalpable drop of their essence, the vast structure of recollection.*

*Remembrance of Things Past, Swann's Way* by Marcel Proust

the movies.) Amnesics have no explicit memory, that is, they cannot consciously recall everyday events. An amnesic would read this article and when questioned later, say she hadn't read it. But if asked something about it—say, if she had ever heard the term memory distortion—she might say that she had and might be able to answer some questions about it, although she wouldn't remember that she knew about it from this article. This is now commonly referred to as implicit memory, a nonconscious form of memory or, as Schacter refers to it, "memory without remembering."

Within this category of implicit memory, Schacter has studied even more refined subcategories, such as a phenomenon called priming—identification of a word or object from "reduced cues." An example of the priming effect is if you're shown a list of words including "table" and later responded to a reduced cue, the letters t-a-b, more often with the word table than if you had not been previously exposed to "table" in the list. Amnesics can complete a cue like this just as a normal person would, but they won't remember seeing the original list or even having been in the research laboratory before (no explicit memory for it).

Schacter and others have explored the various properties that distinguish this priming effect and have found, among other things, that it seems to depend on structures in the brain involved in perception. In PET studies, which show areas of enhanced blood flow in the brain, he and colleague Lynn Cooper at Columbia have found evidence for their claim that the area of the brain involved in priming is the inferior temporal cortex. Skill learning (such as riding a bike), which is another kind of implicit memory, relies on subcortical structures. In contrast, the hippocampus is where blood flow is enhanced when a person is using explicit memory.

These are the kinds of accumulating evidences that have pointed to the concept of memory as a complex reconstruction involving diverse sources in the brain.

Multiple memory systems appear to be involved, which has implications in understanding memory distortion. Also, the kind of tests researchers such as Schacter have been using to test implicit memory may be useful for assessing distortion. Implicit memories do not involve recollection of the source of information, says Schacter, and people may be inclined to generate a plausible—even if inaccurate—source.

"At the conference one of the themes that crystallized was the role of source amnesia in distortion," says Schacter. "Over time people can remember certain aspects of an event, but not whether it was an actual event or imagined, dreamed or told to them."

As a result of the conference, Schacter has become more interested in memory distortion. He has just completed an overview of the history and current status of memory distortion for a book that is emanating from the conference, to be published by Harvard University Press. And he has contributed a paper with Tim Curran on the cognitive neuroscience of false memory for an upcoming issue of the *Psychiatric Annals*, which focuses on false memory.

Just as the dissociations between explicit and implicit memory are providing insights about the nature of perception, memory and consciousness, so might understanding the differences between true and false memories. Schacter is optimistic that the "components of the remembering process that contribute to distorted memories" can be "teased apart" and linked to networks and systems of the brain.

Much as Schacter's professional work is propelled by a purely scientific exploration of memory, he also appreciates the artist's sensitivity for the mysteries of the subject. He and his wife, Susan McGlynn, have collected over 50 pieces of art in various media that incorporate memory in some way as a major subject. In an example of cross-pollenation of science and art, he used the cash prize received from the National Academy of Sciences Troland Research Award (soon after he came to Harvard in 1991 from the University of Arizona) as seed money for this memory-related art collection.

Some of the works were displayed at the memory distortion conference; they were part of a more complete exhibition of his collection at the Newton Art Center in 1993, called Fragile Power: Explorations of Memory. Fragile power to him encapsulates what he calls the paradox of memory function.

As Schacter wrote in the exhibit catalog: "The personal past, though often experienced as ephemeral and distant, is a virtually ubiquitous influence on the present, shaping our current perceptions, feelings, and behaviors in ways that we little understand but cannot escape."

*Ellen Barlow*

# The Curious Cure

*by Gerald D'Arcy Klee*

Ingrid and Otto lived in a modest house in a quiet neighborhood. They had been childhood sweethearts and had married young. Their union was not blessed with children, but it was blessed with a quiet love and companionship. They didn't go out much. They enjoyed sitting at home together in the evenings. They didn't talk much, but they understood each other without the need for words. Faithfully they watched the six o'clock news on television together every evening, followed by their favorite shows, which included "The Honeymooners," "I Love Lucy" and the "Ed Sullivan Show."

After 40 years of marital bliss, Otto died as quietly, and one might say as uneventfully, as he had lived. Hardly anyone noticed, except of course Ingrid. She was devastated. After a small, quiet funeral for Otto, she went home and went into a deep depression. She sat in a chair all day, nervously fidgeting, and would hardly eat or sleep. She was also constantly scared. The slightest sound would send her into spasms of fear that someone was breaking into the house. She seldom went out because that would be too dangerous. She could only sit and sadly wish that Otto were back. If she couldn't have him back, she longed to join him in the grave.

The neighbors brought food, but she hardly touched it and barely spoke to them. Her only living relative, a sister who lived in a neighboring state, visited her and saw that her condition was serious. Before she wasted away entirely, her sister convinced her to see the family doctor who looked her over and found no physical problems other than poor nutrition. He sent her to me for psychiatric care.

I've seen a lot of people in mourning and a lot of people in depression, and a lot of people who were both in mourning and depression. Rarely have I seen a sadder case or one more difficult to treat. Ingrid didn't talk much, hardly at all in fact. She didn't even talk much about Otto. They had never talked much with each other. She just missed him terribly. And it didn't look as if she could live without him.

No medicines helped her. Months went by and things weren't getting any better. In fact, she seemed to get even more depressed as the anniversary of Otto's death was approaching.

On the anniversary of his death, Ingrid visited his grave, as she had often done. She spent a long time there "communicating" with him silently. While she was there, she saw a large brown and black German shepherd who came up to her and licked her hand. He then sat at her side looking up expectantly. Ingrid was surprised to discover that she was not afraid of him. He had no collar or tag. As she left the cemetery, she noticed that he was following close behind her.

After driving home, Ingrid heard a scratching at the door as she sat in the living room. She looked out and there was the dog. She let him in. He went straight to the kitchen and looked up at the sink and then at the refrigerator. Ingrid knew he must be thirsty and hungry so she gave him a bowl of water and some leftover food that the neighbors had brought. After having his fill, the dog went into the living room and sat in front of the television set, his ears alert and his tail wagging. It was just about six o'clock; time for the evening news.

Ingrid hadn't watched television since Otto died. She turned it on and she and the dog watched the news. His attention never faltered. He appeared to show emotions in relation to whatever news stories happened be on at the moment. He even growled at the same politicians Otto had disliked. At eight o'clock, the dog was again sitting in front of the television set with his tail wagging. It was time for the "Ed Sullivan Show." Ingrid hadn't watched that either since Otto had died. So they watched it together and the dog seemed to enjoy it immensely, as did she. Ten o'clock was the "I Love Lucy" show and the same thing happened. Ingrid laughed for the first time in a year.

At bedtime, she crawled into bed, ready for a good night's sleep. The dog climbed into the bed next to her in Otto's place. It seemed natural and they both fell asleep. Ingrid slept through the night for the first time in a year.

The next morning she gave the dog Otto's favorite breakfast—ham and eggs, toast and marmalade and coffee. He gulped it down. They went for a walk. They ate lunch and then dinner. The dog loved all of Otto's favorite dishes.

Ingrid regained her appetite, became relaxed and didn't feel a moment's fear or loneliness. Soon she was calling the dog Otto. Otto was always at her side. Every evening at six o'clock, they watched the news together and later the "Ed Sullivan Show," "I Love Lucy," "The Honeymooners" and all of the other

television shows that Ingrid and Otto used to love to watch together.

When I saw Ingrid again some weeks later, I hardly recognized her. She was back to her normal weight; most of the lines had left her face. She was relaxed and happy. She introduced me to Otto and told me that God must have sent him. I didn't see much of Ingrid after that. Now and then I would run into her in the street, always accompanied by Otto, both of them looking relaxed and happy.

Time went by and Ingrid died. Otto was present throughout the funeral service, which was attended by only her sister and a few neighbors. Of the few friends she'd had, most of them were already dead. She was placed in the earth by the side of her husband. Otto number two remained at the graveside after everyone left. He did not eat or drink or sleep. Soon he was gone and seen no more.

Some people said they had seen him just fade away. Others said they saw him fade into a shadow and saw the shadow rise into the sky and disappear. People say psychiatrists don't have all the answers. I have to admit that's true.

*Gerald D'Arcy Klee '52 practices psychiatry in Towson, Maryland. This story is based on a case he saw some years ago and, in reconstructing the details, says "my imagination may have filled in a few things here and there."*

# What's in a Dream?

*Dreams play a prominent role in the waking life of neurophysiologist Allan Hobson '59, and associate professor of psychiatry, Alfred Margulies '74. While both men ask some of the same questions about this nocturnal phenomenon, their professional approaches and conclusions reflect their different disciplines.*

**Alfred Margulies:**
One of Margulies' primary goals as a psychoanalyst, as described in his book *The Empathic Imagination*, is "to approximate the inner, emotional experience of another, a process of empathy." Dreams are essential to his work because they present a rich clinical opportunity to enter into his patient's world-view. Dreams are one avenue into what he refers to as the "inscape" of another person.

In addition to his associate professorship at Harvard Medical School, Margulies also serves as director of medical student education at Cambridge Hospital. He is currently teaching a dream seminar at the Psychoanalytic Institute of New England. "During the seminar we review Freud's work and the subsequent evolution of the psychoanalytic literature over the past 100 years. We also look at alternative theoretical approaches. In addition, we explore how dreams are currently used in clinical practice," says Margulies.

*continued on page 48*

**J. Allan Hobson:**
J. Allan Hobson and his associate Bob Stickgold's recent invention, the Nightcap, has taken dream research out of the sleep lab and into the home. This shift, say researchers at the laboratory of neurophysiology, has given them far more detailed and far more plentiful dream reports from subjects.

Researchers have also gotten far more sleep. The cloth Nightcap is worn on the head of the sleeper and is attached to a recording instrument that lies under the pillow. Since most dreams take place during the REM stage, researchers used to have to wake dreamers at just the right moment to get fresh reports. The cap can now be programmed to do that work for them.

As a neurophysiologist, Hobson's first interest is in what our nocturnal hallucinations tell us about the brain/mind. He approaches dreams through the activation/synthesis hypothesis, which he and associate

illustration by Manuel King

Robert McCarley developed in 1977. The activation component of this model refers to internally generated brain waves (PGOs) that travel from the brain stem to the thalamus, and are responsible for the brain's frantic nocturnal activity. All during REM stage sleep.

The synthesis process refers to the way in which the brain interprets the multitude of signals generated by brain stem activity. The synthesis component, controlled largely by the forebrain in which memory resides, still contains elements of mystery, as Hobson himself is the first to admit. "Dreaming is chaotic but it also has a lot of order, narrative structure. "Where does [this] narrative structure come from?" Hobson asks. "The honest answer is, we don't know."

While psychoanalysts and psychologists value dreams for their telling variations, Hobson values them for their universality. "The formal qualities of dreams are determined by the brain and nothing else," he says, refering to the brain stem, in part, as the controlling mechanism for sleep and dreaming. "Dreams are visual, people tear around these wild landscapes. They have incomplete arrangements. They're afraid they don't have their passports. They don't have their clothes on....They're all anxious."

Hobson's lab has conducted emotional inventories on dream reports in which anxiety is consistently the leading emotion. "Whether that's a reaction to the bizarre dream content or some parallel process which is initiated on its own is not clear. But that they interact is certain, because when dreams are bad they tend to get worse....Part of what I say in my book about emotion is that—and this is a quarrel with Freud—anxiety is not a symptom. I'm with Kierkegard. Anxiety is a part of life...It's designed to keep people wary," says Hobson. "The brain is an anxiety emitter," he adds, referring in part to his latest book, *The Chemistry of Conscious States*.

Hobson's associate Bob Stickgold, is currently embarking on a recurrent dream study. Says Hobson: "People claim to have the same dream over and over again....But people who have recurrent dreams need to keep dream diaries, so that we have some documentation of this. Are they talking about dreams that are identical or dreams that are similar?...All we know is what people say and we have good reason to be skeptical about that. Not that we distrust it, it's just not adequate."

Unlike sleep, says Hobson, the many "sub-states" of waking make that level of consciousness impossible to describe with the same scientific precision. Future plans for Hobson's lab include looking at the way the brain changes state in the MRI or the PET scan. "It has a relevance to mental illness, of course, because dreaming is a psychotic state."

Hobson is confident "that dreaming is probably the first state of consciousness about which we will have anything like an adequate neurophysiology. We have to develop a state orientation. We have to understand that there are numerous states of consciousness, and that we need to describe them better."

*Margulies continued:*

Margulies' approach to dreams is both literary and scientific: "I will take knowledge wherever I can find it. I think the scientific approach is extraordinarily helpful, but I also think that the nature of subjective experience is to be unique and unrepeatable." And no one better describes subjectivity than the great authors to whom Margulies often refers: "When you look at Proust's *In Search of Lost Time* or James Joyce's *Ulysses* or *Finnegan's Wake*, the spectacular thing about such works of art is that they have the ring of authenticity partly because they are so particular, so idiosyncratic....And it is that very idiosyncracy that is so universal."

For Margulies the act of dream interpretation cuts to the very heart of the relationship between patient and therapist. But while dreams are extremely useful in analysis they are also extremely challenging. In paper, entitled "The Empathic Imagination: Empathy and Inscapes" (published in the *Journal of The American Academy of Psychoanalysis*, 1993), Margulies discusses the complexity inherent in the act of analysis: "My patient tells her story but I, like it or not, hear symbolism and my elaboration in turn affects the patient's experience of her own experience in circular fashion. That is, her symbolism creates a fullness that I the listener hear, even though the implications are opaque to the dreamer herself."

The pure subjectivity of relationships (particularly that of the patient/therapist) fascinates Margulies. He is intrigued by the fact that "when people converse with one another they construct a language of one to the other. My interest in that is not how do you get rid of that [phenomenon], but the fact that we do create this together."

Margulies, like most psychoanalysts, believes that dreams are full of symbols. However, he explains, each person has his or her own set of symbols. "There is no dictionary you can refer to for symbols. As Freud always insisted, one must gather the dreamer's own associations to see what other hidden and deeply personal meanings are implicated. *The Interpretation of Dreams* is not merely about dreams but, more importantly, about the whole question of the unconscious. That is, we are not so aware of why we do what we do—we have a hidden well of complex and conflicted feelings and motivations beneath the surface of experience. And this is Freud's enduring legacy."

Not only are symbols unique to the individual dreamer but they are dynamic in meaning: "One must look at a dream over time. Some dreams and some experiences take a lifetime to understand."

*Sarah Jane Nelson*